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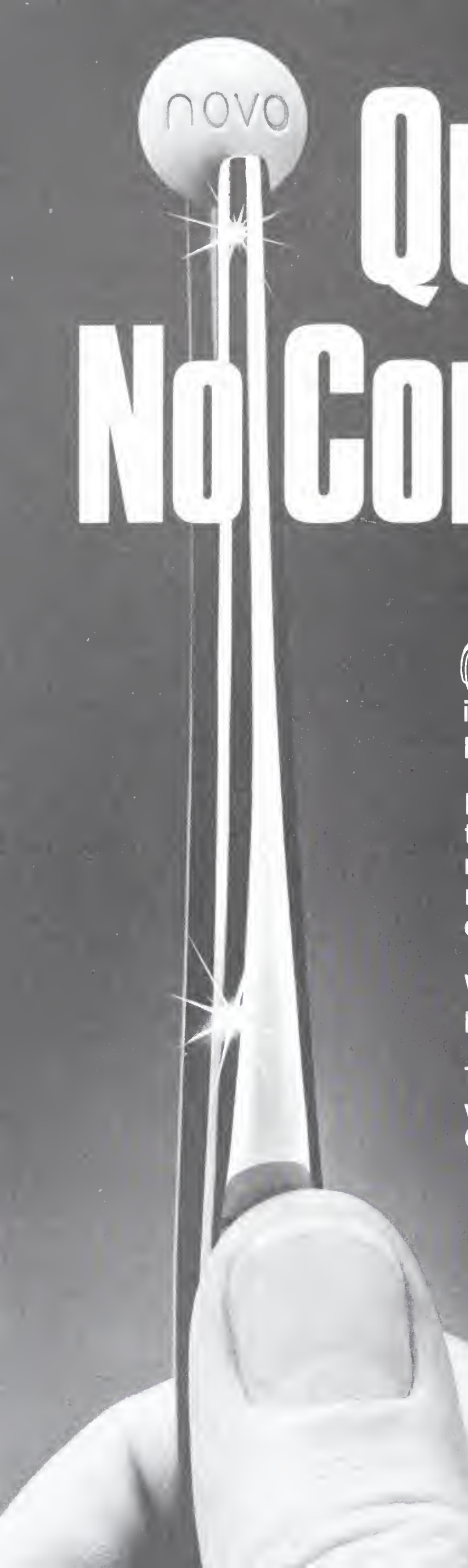
Medical Journal



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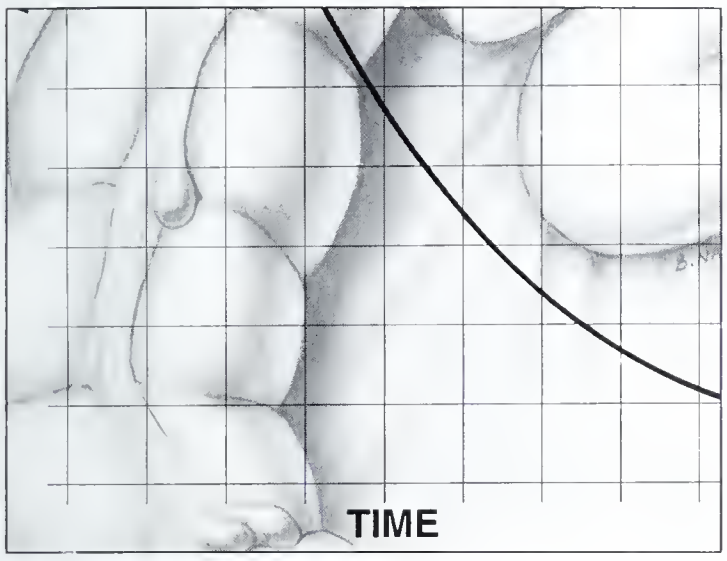

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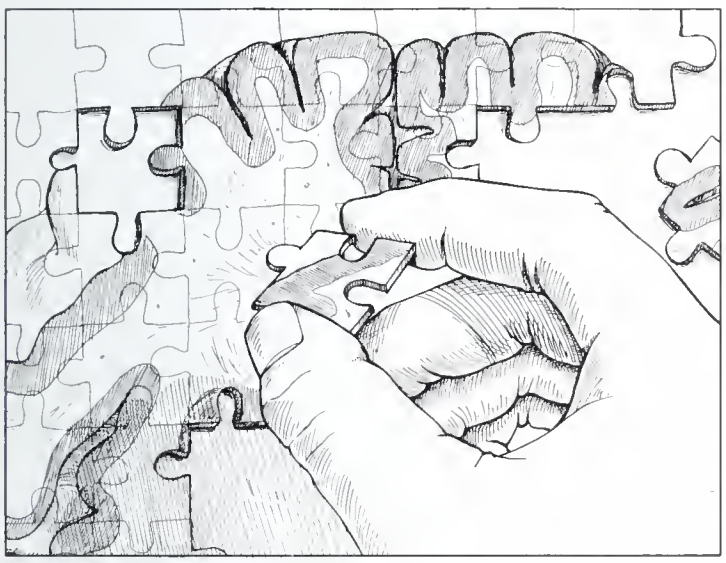

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Front cover designed by Cynthia Yee,
Department of Biomedical Communications,
University of Toronto.

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Editorial

Dear Readers,

We would like to welcome our readers to the UTMJ's 71st year of publication. Our gratitude is extended to our many patrons and subscribers for their generous support. These contributions make it possible for the Journal to continue to showcase the high quality of work being done by medical students at U of T.

On a sadder note, we regretfully announce that our secretary, Mrs. Audrey Randall, is leaving. Mrs. Randall has provided invaluable service, guidance, and advice to the editors of this journal for the past twenty-two years. This publication is indebted to her for her immense contributions; she will be sorely missed.

We would like to acknowledge the hard work and diligent efforts of the Journal staff in helping us put together this first issue. Its contents encompass an eclectic array of topics. The feature article introduces a new technique for knee reconstruction in the field of orthopedics. In contrast, a review article in ophthalmology discusses the uses of botulinum toxin, a medical approach to therapy that is replacing surgery as the treatment of choice for certain oculomotor defects. Of interest to medical and surgical disciplines alike is a review of the GI condition known as short bowel syndrome. In the area of primary care, a discussion of issues surrounding the management of victims of sexual assault is presented. Finally, the realm of brain and behaviour provides the focus for two articles. The pediatric developmental disorder known as Rett Syndrome, a condition that has only become recognized in the past decade, is reviewed. In addition, our News and Views column reports the latest word on the treatment of autism as presented by Dr. Luke Tsai at the international conference held this past summer in Toronto.

We hope this assortment will prove useful and interesting. As always, we welcome any letters or comments from readers.

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Reconstruction of the Posterior Cruciate Ligament Using the Bone - Patellar Tendon - Bone Autograft

John T.C. Lau (9T4) and Richard M. Holtby, M.B., B.S., F.R.C.S.C.

Abstract

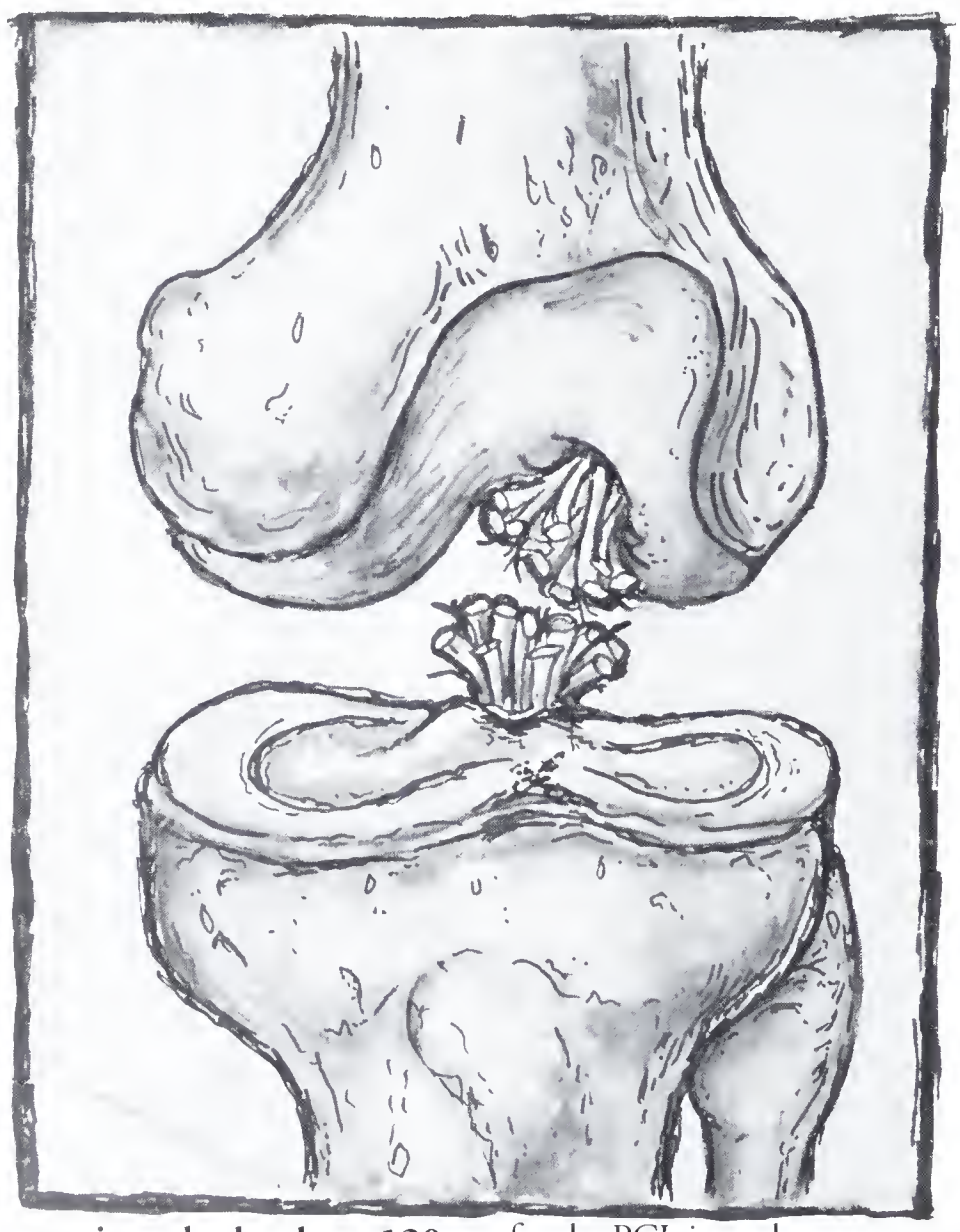
The purpose of this paper is to introduce a procedure for the reconstruction of the posterior cruciate ligament and to examine the results in a trial population of five patients. This procedure restores posterior cruciate ligament function by placing an autogenous bone - patellar tendon - bone graft anatomically through two incisions, using an anterior and posterior approach with immediate bone-to-bone fixation, which provides earlier mobilization, rehabilitation, and recovery than other techniques.

In a trial population of five patients with three isolated and two combined posterior cruciate ligament injuries, the posterior cruciate ligament was reconstructed because of recurring instability. Following the procedure, the median length of stay in hospital was 9 days. By four weeks, all patients were weight bearing as tolerated without a splint, and by three months, four patients had at least 120 degrees of flexion. At follow-up, all patients had a full range of motion and four patients had no episodes of giving way, but clinically detectable posterior instability was still present. The complications of this procedure included one case of deep vein thrombosis, one case of irritation from the screws on the medial aspect of the knee, and two cases of patellar fracture.

Introduction

Posterior cruciate ligament (PCL) injuries are less common than anterior cruciate ligament (ACL) injuries, but the true incidence of PCL injuries is unknown, since some patients are asymptomatic. Some PCL injuries, however, are associated with severe instability and disability. The severity of the symptoms may reflect the extent of the injuries, with isolated PCL injuries producing less instability and disability than more extensive combined injuries with damage to the joint capsule or the postero-lateral complex (consisting of the lateral collateral ligament, the popliteus muscle, and the arcuate fibres of the capsule).

CYNTHIA YEE



Management of injuries to the ACL and of the resulting anterior instability patterns is well understood largely due to the work of D. Macintosh at the University of Toronto[1]. Management of posterior instabilities has not been as reliable partly because of the problem of combined injuries and partly because it is much harder to substitute a graft for the PCL in such a way as to reproduce its function. The femoral origin is extensive with no clearly defined isometric point[2], the position a graft must be placed in so that it remains taut throughout the range of motion. Different fibres of the PCL tighten at different angles of flexion[3,4]. Since most grafts cannot duplicate this property, they will either stretch, causing failure of the graft, or restrict motion.

As a result of these difficulties, the rehabilitation protocols for many described reconstruction techniques have

involved prolonged immobilization of the knee which has produced problems such as stiffness and joint degeneration. In theory, the use of a strong graft like the patellar tendon[5], with bone at either end for immediate rigid fixation, should allow early movement of the knee and better stability, thus improving the results of the reconstruction.

PCL Function and Clinical Assessment

Hughston proposed that the PCL should be considered the primary stabilizer of the knee[6] due to its central location, high tensile strength, and large cross-sectional area[7]. It originates anteriorly at the lateral surface of the medial femoral condyle and extends posteriorly to a depression between the tibial plateaus approximately 1 cm below the tibial surface[8].

The functions of the PCL and other ligaments have been studied by selectively sectioning ligaments and observing the pattern of instability produced[9]. Knee instabilities are classified according to the direction of tibial displacement relative to the fixed femur. The direction of displacement can be: (1) uniplanar, which is purely in one direction (e.g. anterior, posterior, medial, lateral), or (2) multiplanar, which has a rotational component (e.g. antero-lateral)[10]. Instabilities in which the tibia moves backwards in relation to the femur can be divided into uniplanar posterior instability and multiplanar postero-lateral and postero-medial instabilities. Since postero-medial instability is extremely rare, the common clinical problem is differentiating between uniplanar posterior and multiplanar postero-lateral instability. It is important to be able to diagnose posterior or postero-lateral instability in order to determine whether there is an isolated injury to the PCL or a combined lesion with an associated postero-lateral complex injury.

The PCL is the primary restraint to posterior translation of the tibia on the femur, providing as much as 90-95% of the total restraint[11]. Isolated disruption of the PCL produces uniplanar posterior instability without a rotational component. With both knees flexed to 90 degrees, the tibia of the injured side is displaced posteriorly on the femur compared to the normal side, producing a posterior sag. Recognizing the presence of a posterior sag avoids mistaking the correction of the posterior displacement for a positive anterior drawer sign. If both the ACL and the PCL are torn, anterior and posterior instabilities result, which are difficult to diagnose because the neutral position cannot be easily defined. Since there is no rotational component to the instability, performing the posterior drawer test will produce an equal posterior translation regardless of whether the foot is neutral, internally rotated, or externally rotated.

When a rotational component accompanies posterior instability, the postero-lateral (PL) complex is most likely the cause. When the PL complex is damaged, the lateral side may open with a varus stress on the knee primarily due to disruption of the lateral collateral ligament. Since there is also a rotational component, posterior displacement of the tibia on the femur will be even more exaggerated with the foot in external rotation (called the PL drawer test[12]) than with the foot in internal rotation. Another useful clinical test that demonstrates this postero-lateral instability is the reversed pivot shift test[13], which is the reverse of the pivot shift test used for assessing the ACL. These clinical tests appear straightforward, but in reality, distinguishing an isolated PCL injury from a combined PCL and PL complex injury is difficult. Clinically, these injuries may range from a complete tear of the PCL alone to a combined injury of the PCL and PL complex, with differing degrees of severity. The clinical tests described previously have limitations since their sensitivity and specificity are greatest only at the extremes of the spectrum of injuries and are less useful for the other cases.

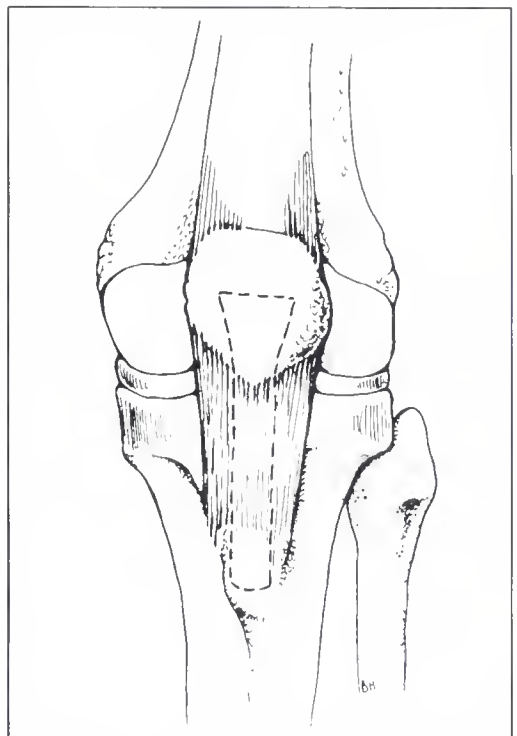


Figure 1: Anterior view of the left knee showing the site where the bone - patellar tendon - bone autograft is harvested.

Materials and Methods

The surgical technique utilized a bone - patellar tendon - bone graft with rigid bone-to-bone fixation at both ends. Under general anaesthetic and with the patient supine, the autogenous bone - patellar tendon - bone graft was harvested from the central portion of the patellar tendon with a proximal patellar wedge and a distal cylindrical block of bone (see Figure 1). A medial parapatellar incision was established. The PCL insertion on the medial femoral condyle was identified and the femoral origin of the graft was established by drilling a 1 cm tunnel passing through the posterior portion of the PCL insertion,

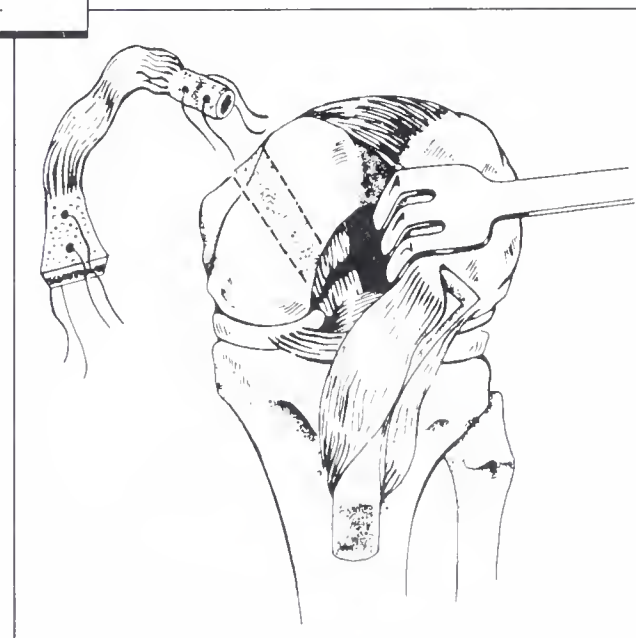


Figure 2: Anterior view of the left knee flexed, with the patella retracted laterally, showing the damaged posterior cruciate ligament and the femoral tunnel as the autograft is being positioned.

which is felt to be the most isometric point. In the left knee, the isometric point is 1 cm posterior to the articular margin in the 9 o'clock position, and in the right knee, the 3 o'clock position. The tibial end of the graft was inserted first and advanced toward the back of the knee (see Figure 2). The wedge from the patellar bone was hammered into the femoral tunnel and when required, interference screws were used to stabilize the graft. Then, with the patient prone, the posterior tibia was exposed through a second incision over the medial head of the gastrocnemius muscle. A longitudinal incision was made in the posterior capsule at the level of the insertion of the PCL and the graft was pulled through. Using a bur, a trough was prepared for the graft in the mid-tibia. With the knee flexed to 90 degrees and using an anterior drawer manoeuvre, the graft was pulled tight, held in place, and permanently fixed with two fully threaded cancellous screws (see Figure 3).

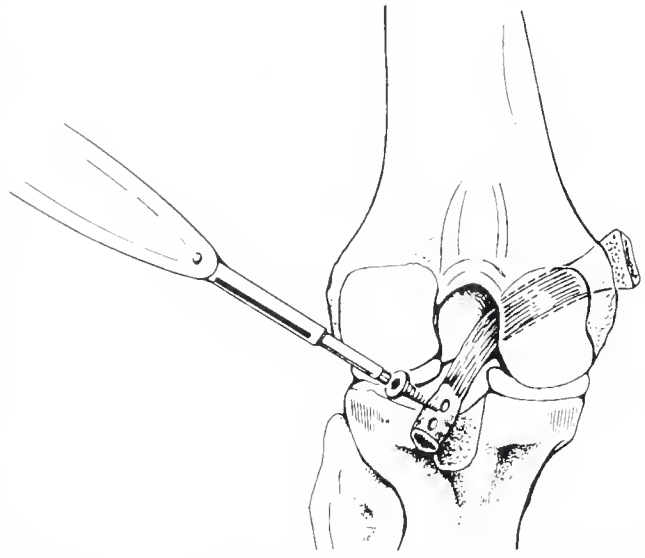


Figure 3: Posterior view of the left knee showing the position of the autograft and the rigid fixation of both the femoral and the tibial ends of the graft.

The trial population consisted of five patients with chronic disability related to PCL injury (4 males, 1 female), ranging in age from 21 to 34 years (average = 29 years) at the time of surgery. All the injuries occurred to the left knee. Four patients were injured while playing sports: 2 skiing, 1 rugby, and 1 parasailing. The remaining patient was injured in a motor vehicle accident. The median time from injury to treatment was 65 weeks (range = 19 to 240 weeks) and the median post-operative follow-up was 13 months (range = 11 to 14 months). In three patients the injury to the PCL was isolated; the other two patients had combined injuries. The patients' clinical examination and pre-operative functional status are listed in Table 1. All patients initially had only their PCL reconstructed.

Table 1: Operative results in the trial population

Patients:	WA	IM	JM	RJ	BC
Injury:	Combined	Isolated	Combined	Isolated	Isolated
Time from Injury to Surgery:	19 weeks	156 weeks	45 weeks	240 weeks	65 weeks
Follow-up:	12/12	14/12	13/12	14/12	11/12
Satisfaction:	Satisfied	Satisfied	Better	Satisfied	Dissatisfied
Lysholm Scores:	59 (85)	44 (93)	38 (43)	38 (89)	42 (87)
Posterior Drawer at 90 degree:	3+ (1+)	2+ (1+)	3+ (3+)	3+ (2+)	3+ (2+)
Posterior Sag:	+ (+)	+ (–)	+ (+)	+ (+)	+ (+)
Reverse Pivot Shift:	3+ (2+)	0 (0)	3+ (1+)	0 (0)	0 (0)
Post-op Range of Motion:	Full	Full	Full	Full	Full
Sports:	None (None)	Full– (Full–)	None (None)	Full– (Full–)	Full– (Full–)
Complications:	None	• Patellar fracture • Painful screws	• Patellar fracture • Deep Vein Thrombosis	None	• Anterior knee pain • Numbness on lateral border of left foot

*Note: Post-operative scores are in parentheses.

The results of the procedure in these patients were evaluated by conducting chart reviews, clinical examinations, Lysholm score questionnaires[14], and in two patients, diagnostic arthroscopies. The patient's chart was reviewed to determine the earliest return to full range of motion and full weight bearing status. Before and after the procedure, the Lysholm score questionnaire was administered. The Lysholm score was based on clinical symptoms and signs: limp; use of a support; stairclimbing; squatting; atrophy of thigh; instability on walking, running, and jumping; pain; and swelling. This generated a score out of 100, with the highest score representing a normal knee. Furthermore, in two patients who had patellar fractures, a diagnostic arthroscopy was performed to evaluate the structural integrity of the graft.

Results

The five patients had a median length of stay in hospital of 9 days (range = 4 to 9 days). At 4 weeks, all patients were weight bearing as tolerated without splint and by 3 months, 4 patients had at least 120 degrees of flexion. At follow-up, all patients had a full range of motion and four patients had no episodes of giving way and felt more stable than before. The patient who still felt unstable had a combined injury to the PCL, PL complex, and ACL and experienced giving way once per week.

Of the four patients who felt stable, all functioned normally in daily activities and three returned to sports. The single patient who still felt her knee was unstable was able to return to her daily activities with some limitations.

Clinically, the posterior sag was eliminated in only one patient. However, the magnitude of the posterior drawer at 90 degrees was reduced in all cases. The reverse pivot shift sign was reduced but still present in the two patients with associated PL complex injuries.

The median Lysholm score pre-operatively was 42 (range = 38 to 59); the patients with isolated injuries had the highest scores. All patients improved their score after the operation, with a median post-operative score of 87 (range = 43 to 93).

The complications observed after this procedure consisted of one case of deep venous thrombosis, one case of irritation from the bone plug on the medial side of the knee, and two cases of patellar fracture in the knee where the graft was harvested. The patellar fractures were treated by open reduction and internal fixation and the medial irritation by removal of the bone spur and the screw. The patient with a combined injury, who still felt unstable, had further surgery to reconstruct her ACL and PL complex.

In the two patients with patellar fractures, diagnostic arthroscopies were performed when the hardware was removed at 7 and 14 months post-operation, respectively.

This revealed intact grafts that were well vascularized by covering synovium.

Discussion

Ideally, for a graft to replace a ligament, it must reproduce the ligament's strength and location. Currently, techniques for reconstruction of the PCL are unreliable[15,16,17]. Our procedure yields results similar to those previously reported, but is still far from ideal. It did, however, allow for early motion and a more rapid rehabilitation.

The results in this trial population are consistent with other published studies using different procedures. Hughston et al.[15] reconstructed the PCL using the medial head of the gastrocnemius followed by plaster immobilization for 6 weeks. From his series of 29 patients, 25 were subjectively satisfied, but all still had a posterior drawer and sag and only 9 patients regained at least 110 degrees of flexion at follow-up. Likewise, Kennedy[16] used the medial head of the gastrocnemius, with a carbon impregnated teflon leader in some cases, and plaster immobilization for 7 weeks. He published a series of 15 patients of which 11 returned to recreational activities, 2 remained unchanged, and 2 became worse. However, all patients had a posterior sag and drawer sign that were reduced. In Clancy's series[17], he used 1/3 patellar tendon placed within a femoral and tibial tunnel, stabilized within the tunnel by tying the ends to buttons. This was followed by plaster immobilization for 6 weeks. In 7 patients with isolated injuries, one patient remained unchanged and six improved, with one patient feeling that his knee was normal. The posterior drawer was eliminated or trace in 6 patients and 1+ in one patient, and only 2 patients lost 10 to 15 degrees of flexion. In 6 patients with combined injuries, all patients were subjectively satisfied, but all patients still had a posterior drawer, ranging from trace in one patient to 1+ in five; 2 patients lost 10 degrees of flexion.

Even though most patients reported better stability with all these procedures, including our own, objective clinical tests still demonstrated instability. With our procedure, more stability was provided for four patients, even though clinically detectable instability was still present. Thus, the improvement in the Lysholm scores post-operatively most likely reflected functional improvement. However, arthroscopic examination in two patients post-operatively revealed grafts that were structurally intact and well vascularized. Thus, since the bone - patellar tendon - bone grafts are viable, improving objective stability may be possible by using a stronger graft, placing it in a more isometric location, and repairing associated injuries. Since all procedures used in PCL reconstruction have failed to provide reliable results compared to techniques used in ACL reconstruction, these obstacles may be common to all such techniques. If future procedures are to provide better results, the biomechanics of posterior instability must be better understood.

Though our results are consistent with existing procedures, the high incidence of patellar fracture is unacceptable. In this study, the incidence of patellar fracture was 40%, compared to 0.3% in ACL reconstructions which use the same autograft. This may indicate higher joint reactive forces in the patello-femoral joint in knees with posterior instability compared to knees with anterior instability. By using a smaller rectangular bone graft, this complication may be prevented; however, this still remains a major concern.

Conclusion

Our study has shown that the technique of bone - patellar tendon - bone PCL reconstruction with rigid bone-to-bone fixation yields results comparable to other techniques with the advantages of early mobilization and rehabilitation. However, it rarely produces normal stability and causes an unacceptable number of patellar fractures. Though this may be a step in the right direction, we are still a long way from solving the problem of posterior knee instabilities.

Acknowledgements

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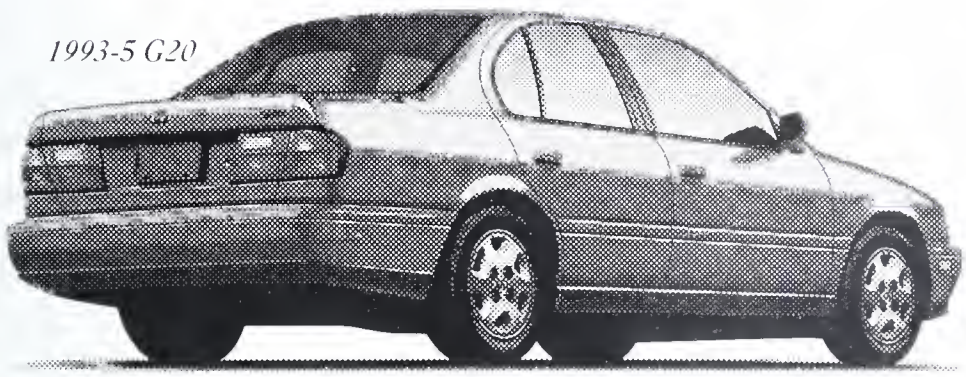

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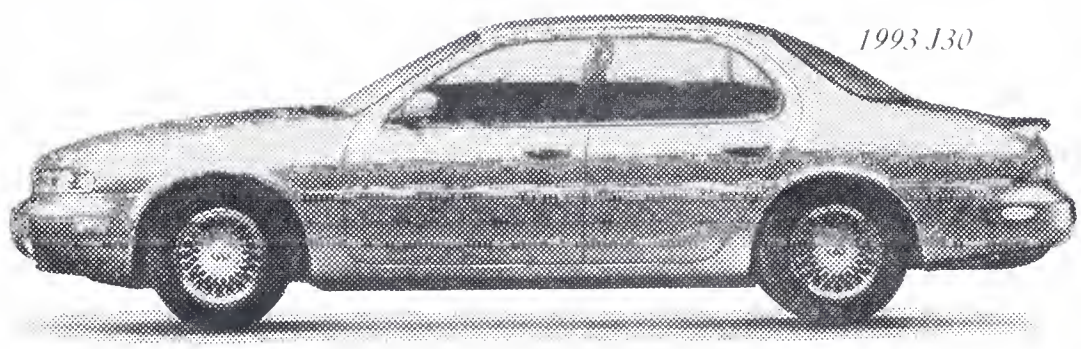

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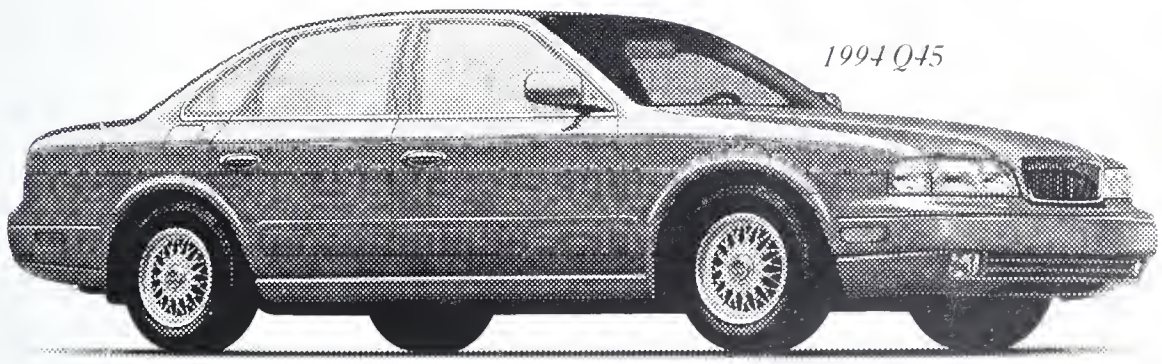

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Short Bowel Syndrome: Current Concepts

Wayne L. Deitel, M.D.* (9T3), Spencer Lister, B.Sc. (9T5), and Bahram Shahi, M.D.**

*PGY-1, Radiology, University of Toronto
** PGY-1, General Surgery, University of Western Ontario

Abstract

Short bowel syndrome (SBS) results from surgical removal or inherent disease of extensive portions of the intestine. Diminished absorptive surface and shortened transit time give rise to steatorrhea and massive diarrhea, which cause short-term water and electrolyte imbalances and long-term malabsorption and weight loss. Loss of the ileum and of the ileocecal valve lead to more severe sequelae. Central to the multitude of pathological mechanisms underlying SBS is bile acid malabsorption; this aggravates fat malabsorption and contributes to massive diarrhea by inhibiting absorption of water and electrolytes as well as inducing active secretion by the colonic mucosa. SBS is further complicated by nephrolithiasis, cholelithiasis and gastric acid hypersecretion. With the onset of SBS, significant adaptation of the remaining intestine occurs under the influence of intraluminal factors (mainly nutrients) and circulating hormones. Management of SBS progresses through three stages. First, fluid and electrolyte imbalances are corrected. Second, the patient is maintained on parenteral nutrition with gradual introduction to oral feeding. Anti-diarrheal medications such as diphenoxylate and loperamide are used to reduce bowel output. Third, the patient is maintained on oral intake if possible and nutritional deficiencies including vitamins (particularly B_{12}) and minerals are detected and corrected.

Introduction

Anatomical or functional loss of massive lengths of intestine as a consequence of surgery or intestinal disease produces a constellation of signs and symptoms known as short bowel syndrome (SBS)[1-3]. This article is offered as a review of the pathophysiologic and clinical aspects of SBS.

Current data suggests 15% of intestinal resections in adults are complicated by SBS; 75% of these cases result from massive resection and 25% result from multiple sequential resections[4]. In adults, massive resection of bowel is most often necessitated by diffuse Crohn's ileocolitis, radiation enteritis, neoplasia, or mesenteric infarction. In infants, SBS is most often a complication of massive intestinal resection secondary to intestinal atresia, malrotational volvulus or necrotizing enterocolitis. Cases of congenital short bowel syndrome have been reported recently[5]. The clinical features of SBS include malabsorption, steatorrhea, acidic diarrhea, and electrolyte imbalance and malnutrition and may involve complications such as nephrolithiasis, biliary stones and gastric acid hypersecretion.

Following extensive resection, the remaining gut begins to adapt in an attempt to compensate[6]. The location and degree of bowel loss, involvement of the small bowel, and presence of a functioning ileocecal valve influence the manifestations of SBS and the extent of compensatory adaptation. When more than 80% of the small bowel is resected, permanent sequelae are inevitable[2]. Resection of the lower ileum limits the adaptation in that the jejunum cannot take over vitamin B_{12} and bile salt absorptive functions. With loss of absorption of bile salts which normally recirculate to the liver (enterohepatic circulation), the bile salt pool diminishes, leading to additional fat malabsorption. Furthermore, the absence of an ileocecal valve allows for the rapid passage of ileal contents into the colon as well as reflux of bacteria-rich colonic contents into the small intestine.

Pathophysiology

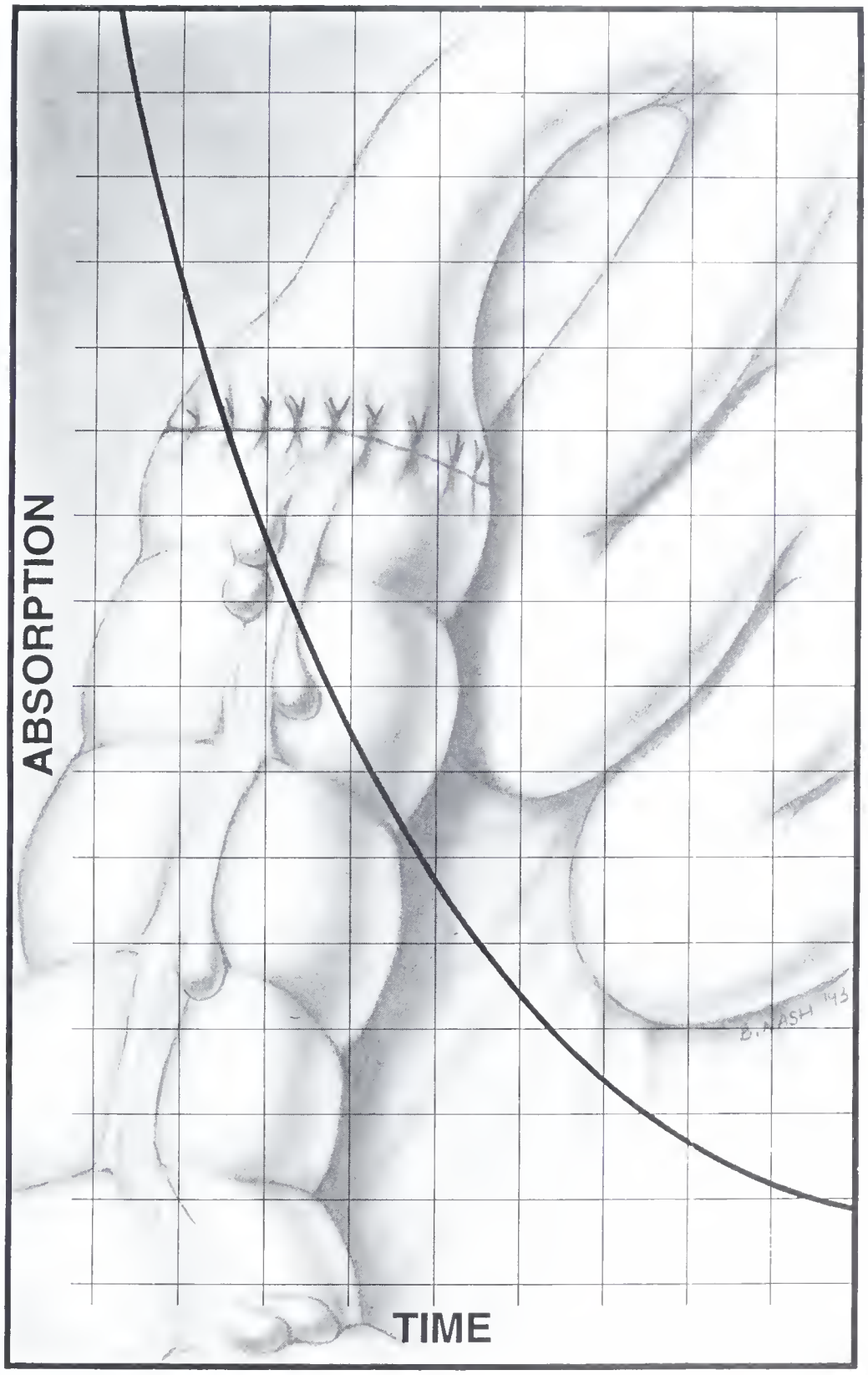
A. Malabsorption and Steatorrhea

Reduction in intestinal mucosal surface area and decreased transit time cause malabsorption, resulting in a negative daily energy balance and weight loss[8]. There is insufficient surface area and time for adequate digestion and absorption of intestinal nutrients. Normally, proximal small intestinal mucosa responds to intraluminal chyme by secreting cholecystokinin (CCK) and secretin which induce pancreatic enzyme secretion, emptying of the gall bladder, and release of an alkaline fluid into the intestinal lumen. In SBS, upper gastrointestinal mucosa may be lost, which results in a blunting of enzyme and alkaline fluid secretion. The situation is aggravated by gastric acid hypersecretion, which lowers luminal pH and inactivates those pancreatic enzymes that do reach the lumen of the intestine.

Normally, bile salts are absorbed by the distal ileum; when it is resected, severe bile salt deficiency results as bile salt

loss greatly exceeds the capacity of the liver to synthesize new salts. The ability to absorb fat and fat-soluble vitamins (A,D,E,K) is dramatically reduced[3]. Steatorrhea ensues along with subclinical deficiency of fat-soluble vitamins. The ileocecal valve normally prevents reflux of colonic contents into the small intestine; when absent, there is reflux and overgrowth in the small bowel of colonic bacteria which then consume nutrients, deconjugate bile salts and irritate the colonic mucosa.

The terminal ileum brush-border is the exclusive site of vitamin B_{12} absorption. Normally, intrinsic factor from the stomach complexes with extrinsic factor (cobalamin) and binds to a specific receptor on the ileocyte. Cobalamin then traverses the cell, accesses the circulation, and is stored in the liver. Although hepatic stores of B_{12} considerably exceed daily requirements for the vitamin, megaloblastic anemia and subacute combined degeneration of the spinal cord will occur after a three year absence of B_{12} from dietary sources. Patients with resections of the distal ileum therefore require periodic injections of vitamin B_{12}[12].



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B. Diarrhea

The diarrhea of SBS is severe and leads to several physiologic disturbances. Unabsorbed nutrients and electrolytes in the gut create a hyperosmotic state, thereby dragging water from the extracellular fluid into the lumen[7]. This results in fluid and electrolyte losses that must be monitored and replaced. Feces consisting of partly digested chyme are voluminous and formless. The acidic pH and digestive enzymes of the excrement excoriate the anal skin. Bacterial fermentation of undigested sugars produces CO_2 and bloating[7].

Bile acids, normally reabsorbed in the distal small bowel, enter the colon. Colonic bacteria deconjugate the unabsorbed bile acids (cholic acid and chenodeoxycholic acid) to form deoxycholic and lithocholic acid, respectively[8,9]. The bile acids hamper absorption of water and electrolytes by the colonic mucosa and induce a secretory diarrhea through mechanisms at the cellular level which may include the following: 1) direct activation of adenylate cyclase leading to increased mucosal cAMP; 2) increase in Ca^{2+} permeability; 3) prostaglandin synthesis and release, ultimately resulting in increased cAMP; and 4) activation of local nervous reflexes[9,10]. Dihydroxylated bile acids (chenodeoxycholate) with hydroxyl groups in the alpha position on the sterol ring are noxious to colonic mucosa[9]. Although both conjugated and unconjugated bile acids cause diarrhea, those of the unconjugated variety are more poorly tolerated. Moreover, hydroxylated fatty acids (e.g. hydrostearic acid, which is chemically similar to ricinoleic acid, the active agent of castor oil), produced by the action of bacteria on unabsorbed food, irritate the colonic epithelium[3,10].

C. Hypersecretion of Gastric Acid

Massive resection of the small intestine, particularly when the proximal portion is involved, results in increased gastric acid output[2,6]. This effect generally resolves within a few months. The pathophysiologic mechanism underlying the hypersecretive phenomenon remains to be explained. Normally, acid secretion is controlled by the action of gastrin, histamine and local acetylcholine (released by parasympathetic nerve terminals) on the parietal cell[13]. In SBS, gastrin levels are increased[2]. Various inhibitory substances, such as somatostatin, gastric inhibitory peptide and

neurotensin are produced by the normal intestinal mucosa[11]. It may be speculated that their absence tips the balance in favour of acid secretion by the gastric mucosa.

D. Nephrolithiasis

Normally, oxalate reaching the colon is bound to calcium to form insoluble calcium oxalate (which cannot be absorbed). In SBS, unabsorbed fatty acids competitively bind calcium and oxalate is thus available for absorption[10]. Unabsorbed bile acids and fatty acids in the colon increase the permeability of colonic mucosa and damage epithelial cell membranes, further enhancing oxalate absorption. Increased intestinal oxalate absorption and increased blood oxalate concentration lead to the formation of renal calcium oxalate stones in 10% of patients with SBS[3].

E. Cholelithiasis

As a result of deficient lower ileal absorption, the body pool of bile salts is reduced to the quantity that can be synthesized between meals. The normal balance of cholesterol and bile salts in bile fluid is thus distorted such that there is a higher proportion of cholesterol, favouring gallstone development.

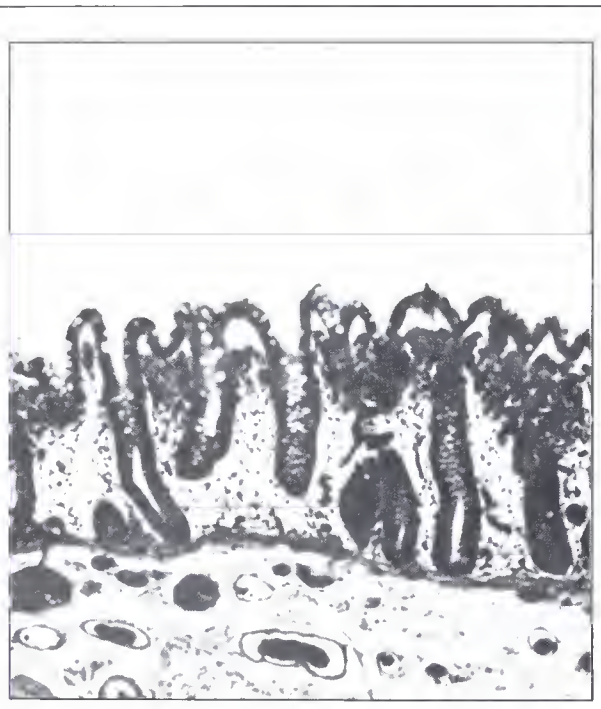

Figure 1 (Left): Normal jejunum at time of resection for a mesenteric vascular occlusion.

(Right): Jejunum from same patient 2 years later, showing very tall villi indicative of absorptive adaptation due to hyperplasia of epithelial cells. (H & E, 75x)

Adaptation

Massive resection of the small intestine is followed by remarkable adaptation of the remaining intestine[6]. The process of adaptation commences immediately after bowel resection and continues for many months until maximum adaptation is achieved. Once the mucosa has adjusted to the new conditions, the following changes to the mucosa become apparent: 1) lengthening and dilatation of the remaining gut; 2) increased height and thickness of small intestinal folds (plicae circulares or valvulae conniventes); 3) increased height and thickness of the villi, despite no change in the density of villi; 4) increase in depth of the crypts of Lieberkuhn; and 5) epithelial cell hyperplasia, which accounts for the other changes mentioned above (Figure 1)[7,14].

The extent of adaptation and whether it will be able to compensate for the pathophysiological derangements (malabsorption, steatorrhea, and diarrhea) depend on the extent and site of resection. At least 80 cm of distal ileum is necessary for complete absorption of bile salts and vitamin B_{12}[2]. In children, the remaining gut is better able to adapt because the intestine grows as the child ages[16].

Factors Affecting Adaptation

A. Intraluminal Factors

Nutrients in the lumen of the gut, especially carbohydrates and amino acids, are the most important stimuli for rapid hyperplasia of the intestinal mucosa[6,14]. For all commercially available formulas, sustained total parenteral nutrition (TPN) is incompatible with mucosal adaptation[2]. Patients should be introduced to an oral feeding regimen as soon after the onset of SBS as possible.

Intraluminal infusion of carbohydrate solutions stimulates mucosal growth, while non-absorbable sugars such as mannitol fail to produce this effect[6]. Disaccharides have stronger stimulatory effects than monosaccharides. Similarly, instillation of amino acids into the gut, even in low concentrations, leads to enhanced mucosal growth[6]. Current studies of glutamine-enriched TPN suggest that this amino acid may be trophic for the enterocyte.

Data concerning the effects of lipids on growth of the intestinal mucosa are somewhat inconsistent. In particular, beneficial effects of long-chain triacylglycerols versus medium-chain triacylglycerols and short-chain triacylglycerols (SCTs) are controversial. Recent studies indicate a positive stimulatory effect of SCTs on the adaptive growth of jejunum, ileum and colon[15].

At least one non-nutritional element of the diet, fibre, has been shown to be effective in inducing adaptive changes[6].

Pancreaticobiliary secretions, in response to chyme-induced release of CCK and secretin from the mucosa of the small bowel, promote adaptation[6]. Other secretions of the GI tract, notably epidermal growth factor secreted by salivary glands, biliary epithelium, and duodenal mucosa, have been found experimentally to induce hyperplasia in the mucosa of the remaining gut[6].

B. Circulating Hormones

Hormones have a role in the adaptation process: CCK, secretin and enteroglucagon are most frequently cited to be involved[9]. Circulating enteroglucagon increases after bowel resection and has been shown to induce hyperplasia of the intestinal mucosa[14]. CCK and secretin likely exert an indirect effect on adaptation by stimulating pancreatic secretion and enteroglucagon release[6]. Other factors affecting adaptation may include corticosteroids, prostaglandins, plerocercoid growth factor and growth hormone[6,14].

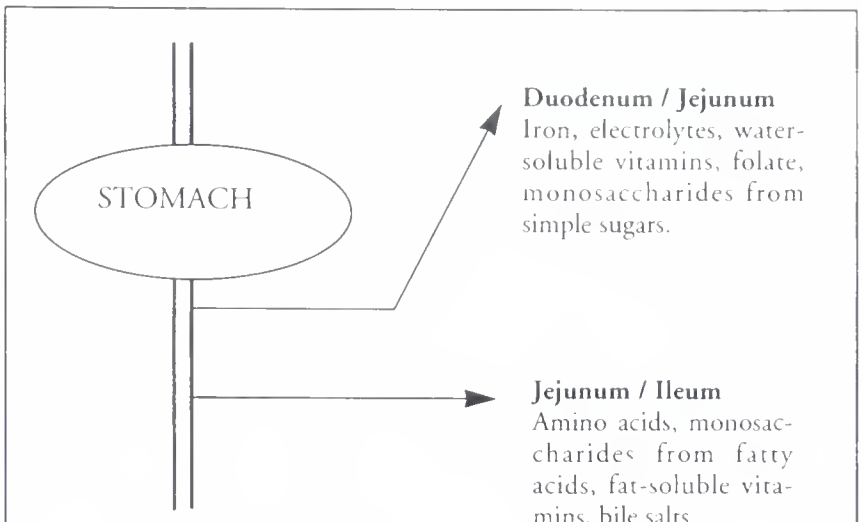
STOMACH
Duodenum / Jejunum
Iron, electrolytes, water-soluble vitamins, folate, monosaccharides from simple sugars.
Jejunum / Ileum
Amino acids, monosaccharides from fatty acids, fat-soluble vitamins, bile salts.

Figure 2: Nutrient absorption in the normal GI tract.

Subcellular Mechanisms of Adaptation

The precise mechanisms through which trophic factors affect intestinal epithelial cells are poorly understood. Mucosal hyperplasia is one empirical sign of adaptation, thus it is not surprising that the amount of enterocyte DNA and DNA replication enzymes increases on introduction of the stimulatory factors[14]. Recent studies have shown that the activity of ornithine decarboxylase, a key enzyme in the synthesis of polyamines such as putrescine, spermine, and spermidine, increases sharply in response to the factors causing hyperplasia of the intestinal mucosa[6,14]. Since polyamines are well-recognized indices of cell regeneration and proliferation, ornithine decarboxylase has been proposed as a point of control in the mechanism of factors that stimulate adaptive changes in the small intestine in SBS.

Management

Patients with SBS are managed medically. They progress through three stages, each requiring different modes of treatment. Stage I, immediately after resection, is characterized by marked fluid and electrolyte loss due to voluminous diarrhea lasting from weeks to months[1,2]. Careful monitoring of intake, output, and serum electrolytes is mandatory in order to avoid severe hypokalaemia and dehydration. Later, a fall in serum calcium, magnesium and phosphate ensues; these electrolytes must be included in the intravenous solutions to avoid a decrease in their concentrations over time.

Most of the adaptive changes occur in stage II, which is characterized by persistent diarrhea and steatorrhea in a patient being nutritionally supported with TPN. Treatment consists of an incremental decrease in the degree of parenteral nutrition with a concomitant increase in oral nutritional intake and clear fluids. The diet must be under constant review and modification to provide sufficient energy and nutrition while minimizing diarrhea[1]. Amino acids and fats are added to promote maximal adaptation. Vitamins and drugs which decrease motility, such as diphenoxylate and loperamide, may be useful. Cholestyramine, which binds to bile acids that irritate the colon, may be helpful but has the undesirable side effect of augmenting steatorrhea.

Once maximal adaptation has occurred, the patient has reached stage III. Stage III is characterized by stable body weight, mostly oral alimentation, maximal fat absorption and minimal diarrhea and steatorrhea[1]. Three months to 2 years may pass before the patient reaches this stage. However, patients with less than 50 cm of small intestine, or those with slightly longer segments but lacking an ileocecal valve will likely require TPN for the remainder of their lives.

Table 1: Stages, features and treatment principles of SBS

Stage	Features	Treatment Principle
I	Fluid and electrolyte losses. Voluminous diarrhea.	Monitor intake, output, electrolytes. Initiate TPN.
II	Persistent diarrhea and steatorrhea in a patient on TPN.	Gradually decrease the degree of parenteral nutrition, while increasing the degree of oral nutrition and fluids Add amino acids, fats, vitamins. Anti-motility drugs (loperamide).
III	Stable body weight, mostly oral alimentation. Diarrhea and steatorrhea minimal.	Adaptation maximal.

Surgical Intervention

Surgical management is largely experimental; it has been undertaken (rarely) in those patients who cannot tolerate permanent TPN[4]. The operations described include intestinal recirculatory loops, anti-peristaltic (reversed)

segments, colon interposition, ileocecal valve reconstruction and bowel transplantation. A consistently safe and successful method for surgically treating SBS has yet to be demonstrated.

Conclusion

Short bowel syndrome is the most devastating consequence of massive intestinal loss. It is characterized by malnutrition, weight loss, steatorrhea, diarrhea, and electrolyte imbalance. Other features include nephrolithiasis, cholelithiasis and gastric acid hypersecretion. Functional and structural adaptation of the remaining intestine occurs, allowing the diarrhea and malabsorption to improve within a few months, provided that nutrients are supplied. The degree of functional improvement achieved depends on the extent and site of resection, the presence of a functioning ileocecal valve and the degree of structural adaptation. SBS is currently managed using a medical approach consisting of intravenous maintenance of electrolyte balance and TPN, with incremental introduction to oral feeding at the earliest possible stage of the disease process. Surgical treatment strategies, to date, have not progressed beyond an experimental stage.

The disturbances to normal physiology in SBS are profound. While the clinical symptoms of SBS will improve over time, the difficulties in treating the condition demand that the prevention of SBS take a high priority. When SBS is unavoidable, a diligent approach to its management will maximize the quality of the outcome.

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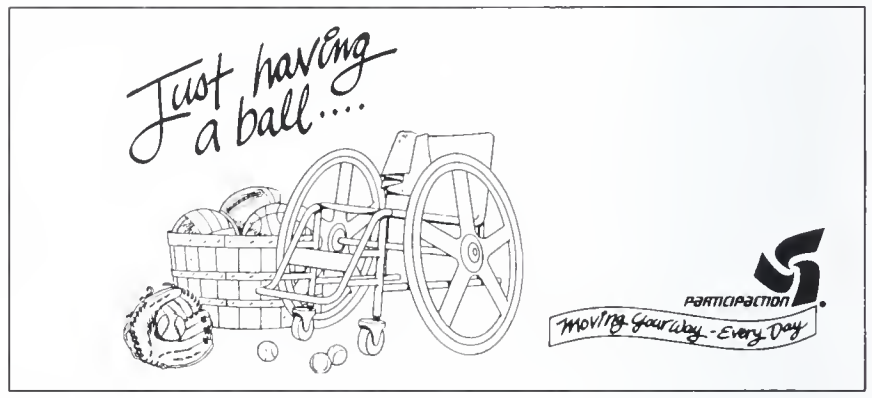

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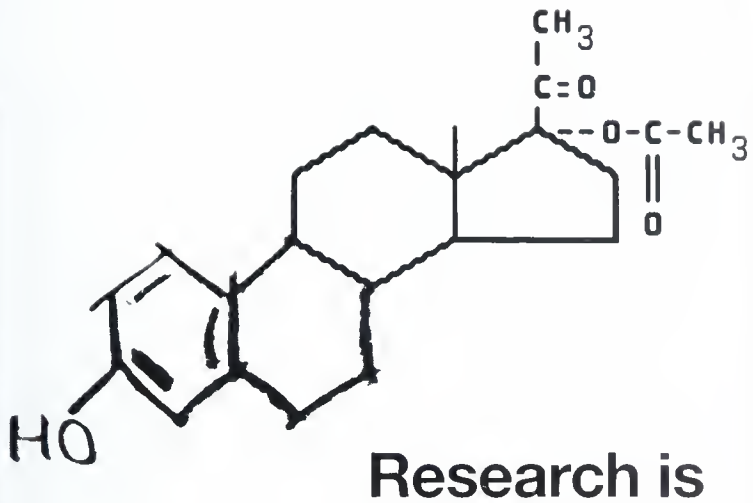

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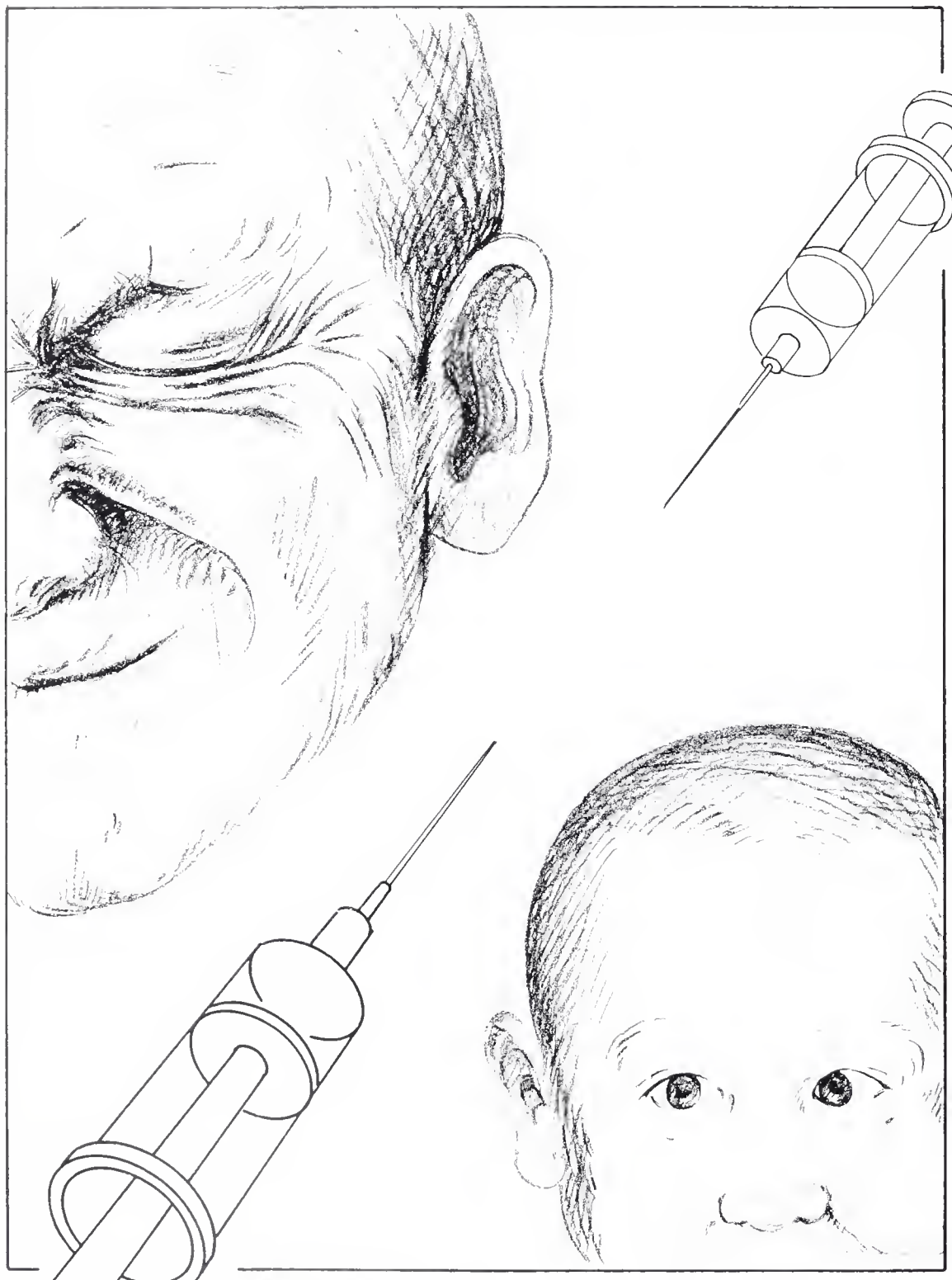
Botulinum A Toxin in the Treatment of Strabismus and Facial Dystonias

Dan DeAngelis (9T4), Stephen P. Kraft, M.D., F.R.C.S.C.*

*Assistant Professor, Department of Ophthalmology, University of Toronto



Abstract

After its introduction in 1978 as a treatment for strabismus, botulinum A toxin has been successfully used to treat a variety of both ophthalmic and non-ophthalmic neuromuscular diseases. We review the mechanism of action of botulinum A toxin. In addition, we discuss the therapeutic indications for the use of botulinum A toxin in strabismus and facial dystonias and the results of therapy with this drug.

Introduction

The use of botulinum A toxin in the treatment of eye disorders was pioneered by Dr. Alan Scott, who in 1978 introduced it as a treatment for strabismus[1,2]. Several years earlier, Behrens first suggested injecting pharmacotherapeutic agents into extra-ocular muscles to achieve transient or prolonged paresis. His initial trials employing alcohol were not successful, the results being either partial and transient or absolute and permanent muscular paralysis[3,4,5]. Studies undertaken by Scott and his group in 1972 utilized other pharmacologic agents such as di-isopropyl-fluorophosphate (DFP) and Bungarus neurotoxin (cobra toxin), attempting to induce extraocular muscle paresis in rhesus monkeys. These agents were found to be inappropriate for use in eye disorders due to systemic toxicity and other local and systemic problems.

It was not until Scott took the most potent toxin known to humans, botulinum toxin, diluted it, and injected it into the extra-ocular muscles of rhesus monkeys that promising results were noted. His data suggested that the toxin's properties were ideal for producing transient weakness of ocular musculature, thereby inducing permanent changes of ocular alignment without causing serious side effects[4]. The first human studies with botulinum toxin were undertaken by Scott and his colleagues in 1978. Preliminary reports indicated that botulinum A toxin injections into extra-ocular muscles were an effective alternative to eye muscle surgery in some cases of strabismus[1,2]. Over the past 15 years, botulinum A toxin has proven to be an effective treatment for some forms of strabismus,

blepharospasm, facial dystonias and other ophthalmic and non-ophthalmic conditions[6-12].

Pharmacology

Clostridium botulinum, a heterogenous group of anaerobic gram-positive spore-forming organisms, is ubiquitously found in soil environments throughout the world. It elaborates the most potent bacterial neurotoxin known. It is estimated that one gram of the crystalline toxoid has the potency to poison fifty million people. The neurotoxins produced by *C. botulinum,* classifiable into eight immunologically distinguishable subtypes (A,B,C_1, C_2,D,E,F,G), have similar pharmacological properties[13]. Toxicity in humans is most commonly attributed to strains A,B,E, and F.

The highly potent toxins of this organism are structurally specific proteins with inherent differences in receptor site affinities[13]. Botulinum toxins are synthesized intracellularly as single chain polypeptides during bacterial growth and subsequently released into tissue fluids when cell growth ceases and the Clostridia undergo autolysis. Evidence that toxin titre continues to increase after complete and total autolytic activity ceases suggests that the toxins are initially released from cells as a relatively inactive precursor, later achieving full neurotoxic activity only after exposure to proteases produced by the cell[13]. The toxin resists degradation by acid and proteolytic enzymes, but can be rendered inactive by heat at 100°C for 10 min, achieved with routine home cooking. In contrast, the spores of *C. botulinum* are highly heat resistant, requiring exposure to temperatures of 120°C, commonly achieved in pressure cookers, in order to be inactivated.

Type A toxin has been the most widely investigated toxin and the first one obtained in a highly purified stable crystalline form[7]. Botulinum A toxin has a molecular weight of 900,000 daltons and is composed of two subunits that readily dissociate in solution. Each subunit is composed of three polypeptide chains: one moiety possessing neurotoxic activity, one moiety possessing haemagglutinating activity, and one physiologically inert moiety. The neurotoxic portion of botulinum A toxin is a single polypeptide chain composed entirely of amino acid residues, having a molecular weight of 150,000. The type A neurotoxic subunit contains four sulfhydryl groups and one disulfide bond. Reduction of the disulfide bonds is purported to abolish all biologic activity.

The toxin used in medical treatments is supplied as a lyophilized preparation in vials containing 40 to 50 nanograms of purified botulinum A toxin. The crystalline complex is reconstituted with sterile saline, and small aliquots are injected into the muscles to be weakened.

Action of the toxin

Botulinum toxin specifically inhibits acetylcholine release at the presynaptic cholinergic nerve endings, such as those found in the myoneural junction and other peripheral cholinergic sites[2,15-17]. Within the autonomic nervous system, sites susceptible to the toxin include ganglionic nerve endings, post-ganglionic parasympathetic nerve endings, and specific post-ganglionic sympathetic nerve terminals. Botulinum toxin does not cross the blood-brain barrier to act on the central nervous system, except in excessively high doses[16].

The paralytic effect induced by botulinum toxin does not interfere with the propagation of impulses in the nerve trunk, nor does it inhibit the synthesis and/or storage of acetylcholine[13]. Furthermore, it does not block the entry of calcium into the nerve terminal. The toxin acts on or in the nerve ending to antagonize those events that are triggered by calcium and culminate in neurotransmitter release[14].

The pharmacokinetics of botulinum toxin action at the molecular level involves three discrete steps (Figure 1). The receptor for botulinum toxin has yet to be identified. The molecular binding, comprising the first step in its action (Figure 1a), is known to be rapid and irreversible, yet it is accessible to inactivation by antitoxin[13]. The second step involves internalization of the toxin (Figure 1b), a stage where antitoxin is no longer effective at reducing the compound's toxicity but no signs of paralysis have yet manifested themselves. This step is thought to be mediated either by adsorptive pinocytosis or the creation of a protein channel through which the toxin passes[13]. Neither

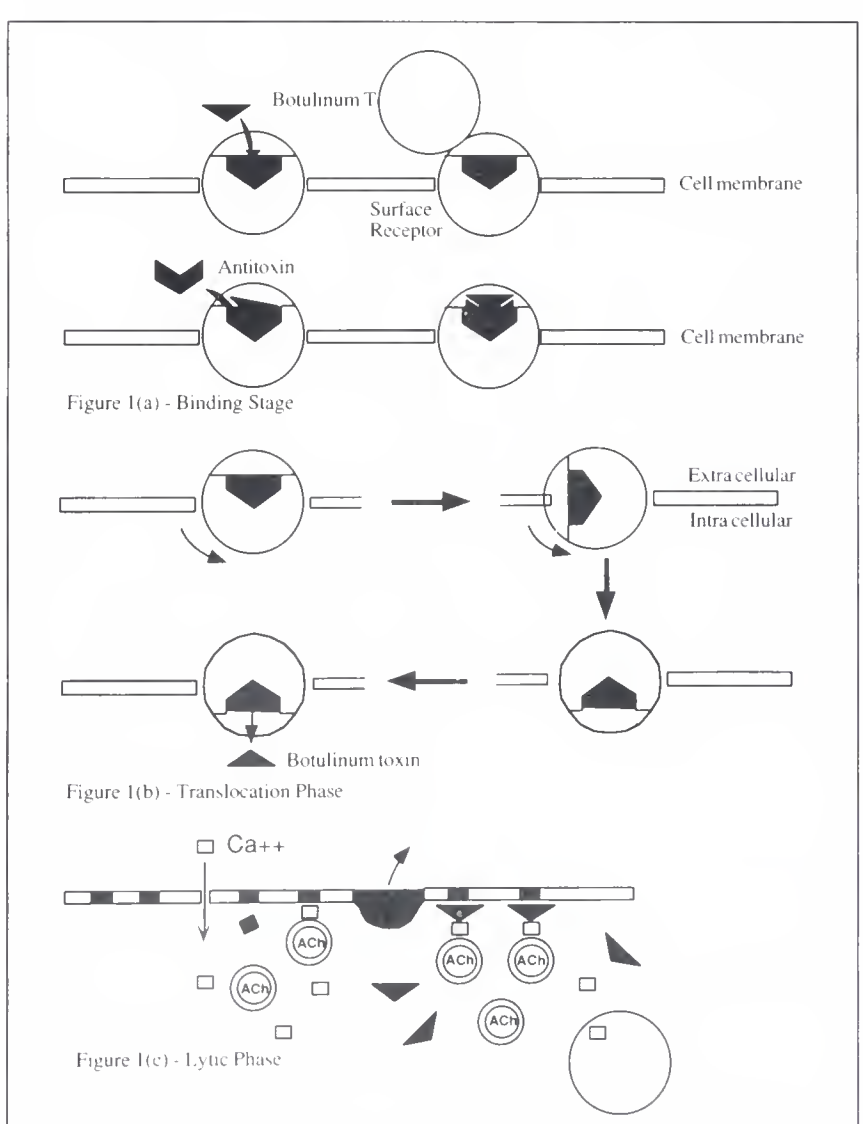


Figure 1: The molecular action of botulinum A toxin.
(a) binding of the toxin to specific cell surface receptors
(b) internalization of the toxin
(c) blockade of quantal acetylcholine release

Table I

Indications for Botulinum Toxin Injections in Strabismus

Horizontal, non-paralytic, non-restrictive strabismus (esotropia, exotropia) Less than 40 prism diopters of deviation Surgical undercorrection and overcorrection
Vertical, non-paralytic, non-restrictive strabismus (hypertropia)
Acute or chronic third and sixth nerve palsies
Restrictive strabismus caused by acute dysthyroid myopathy
Inflamed or pre-phthisical eyes
Strabismus following retinal detachment surgery
Surgical correction contraindicated or refused

of these first two steps alter neuronal function. The last step in toxin kinetics involves the blockade of impulse-induced neurotransmitter release. The intracellular action is thought to be due to the effects on calcium and excitation-secretion coupling. One of the known functions of calcium at the nerve terminal is to promote the ability of acetylcholine-containing vesicles to fuse with specialized membrane sites and secrete their stores of acetylcholine (Fig 1c). By inhibiting presynaptic vesicular fusion, botulinum toxin thus impairs the quantal release of acetylcholine.

Consequences of blockade

When injected intramuscularly at therapeutic doses, botulinum toxin produces transient weakness due to localized chemical denervation. Histopathologically, the results of this denervation include muscle atrophy and some demyelinative changes with a concomitant increase in the number and distribution of acetylcholine receptors[5]. There is some evidence that the nerve roots can sprout and reinnervate the muscle, suggesting that weakness is reversible. The degree of paralytic action of botulinum toxin is dose-related, with the peak effects seen five to seven days after injection. The time to recovery from the toxic effects ranges anywhere from six to ten months[4,5,14,15], after which point the muscle may or may not regain complete function.

Strabismus

Strabismus is an ophthalmological condition in which the eyes are misaligned. It is the second most common eye problem seen in children, and can be either congenital or acquired. It may be classified into (1) paralytic strabismus, in which one or more muscles are weakened such that their normal action is rendered impaired by faulty innervation, and (2) non-paralytic strabismus, wherein the ocular muscles receive normal or excessive levels of innervation.

Treatments for strabismus

In children, accurately prescribed spectacles to correct refractive errors are the most important intervention in the treatment of strabismus. Improvement of focused retinal image with spectacles allows for optimal binocular fusion. Prisms, which alter the direction of incoming light to eliminate diplopia, can be used in some cases. Cholinergic agents can also be used in the treatment of childhood strabismus by altering the accommodative power of the eyes. Other treatment modalities used in children include eye patching to correct amblyopia and eye muscle exercises.

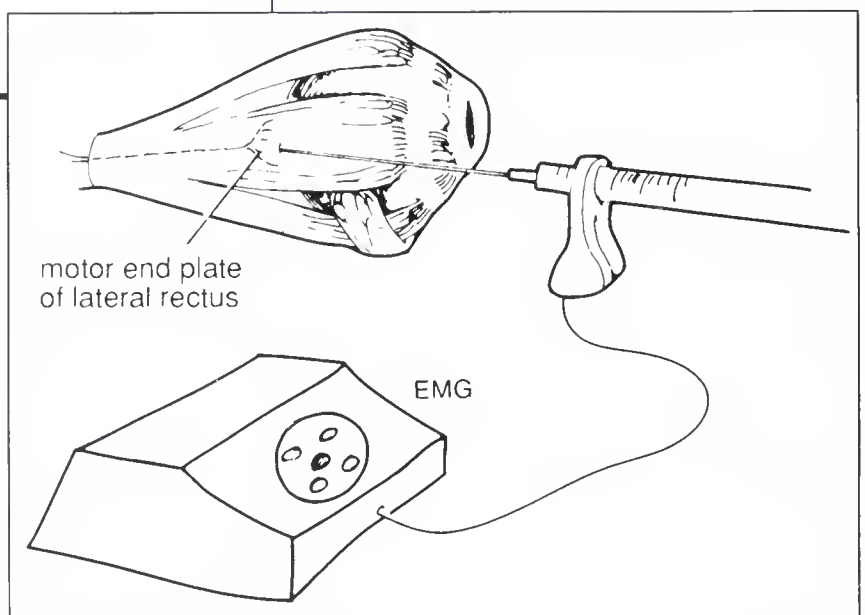


Figure 2: Diagram illustrates technique for injecting lateral rectus muscle. Injection is performed using long 25- or 27-gauge needle which is inserted in the area of the end plate of the ocular muscle. Muscle activity is recorded with an electromyographic device connected to the injection apparatus.

Strabismus in adults most frequently presents as either uncorrected strabismus acquired in childhood or secondary to muscle palsies or mechanical restriction subsequent to trauma or neurological conditions. Treatment with prisms is the most popular non-surgical means to correct strabismus in adults. Other interventions have included exercises to restore normal coordination of eye muscles, or "occlusion" of the misaligned eye to eliminate diplopia[15].

Surgical correction is considered if the strabismus is refractory to non-surgical treatment. Surgical approaches include weakening or strengthening one or two muscles, and may include the use of adjustable sutures.

Botulinum treatment of strabismus

The availability of botulinum toxin injection to treat strabismus in both adults and children has provided an effective alternative for some individuals who would have otherwise had no other options but surgical intervention. The ophthalmic indications for the use of botulinum toxin are outlined in Table I[20]. At the present time, the only contraindication to its use in strabismus is a known hypersensitivity to any ingredient in the formulation (botulinum toxin type A, human albumin, sodium chloride). The drug has not yet been formally approved by Health and Welfare Canada for use in children under 12 years of age.

Method of Treatment

To prepare the eye for injection, several drops of a topical anaesthetic are administered to both eyes. An injection of

botulinum toxin is prepared by drawing into a sterile 1.0 mL syringe a small aliquot of reconstituted toxin. The dosages of toxin for strabismus range from 1.0 to 5.0 nanograms, depending on the size of the angle of misalignment. The syringe is attached to an electromyographic (EMG) needle, which is connected to an EMG recording device (Figure 2). The needle is inserted subconjunctivally, behind the muscle's insertion on the globe. The eye is then turned towards the muscle to activate the motor units. The needle tip is advanced further into the muscle under the guidance of the signal transmitted from the needle tip, until the nerve-muscle junction in the muscle belly is reached. It is this area, at which the surgeon hears the increase in EMG activity, where the neuromuscular junctions of the singly innervated muscle fibres are concentrated[2]. The toxin is then injected into the muscle, and the needle is withdrawn. The patient is permitted to leave after a short waiting period, ensuring that there are no immediate allergic reactions or bleeding.

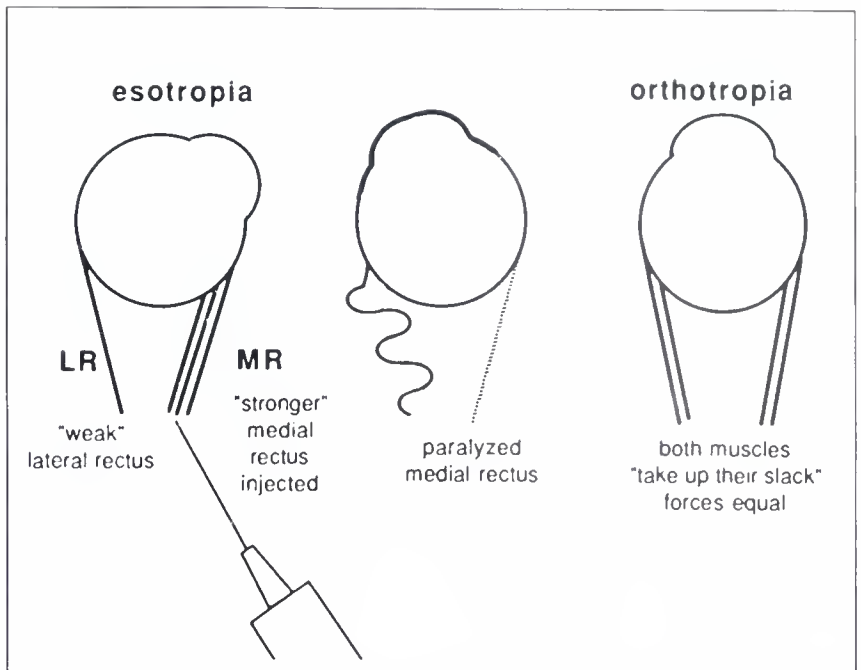


Figure 3: Principle of aligning crossed eye (esotropia) with botulinum injection. Injection of stronger medial rectus (left). Induced overcorrection due to medial rectus paralysis (center). Eyes are straight (orthotropia) with balanced muscle forces (right).

The goal of treatment in strabismus is to restore the balance of forces to the muscles of the misaligned eye. The injected muscle becomes paralyzed and will, over the course of several weeks, become slightly atrophied, elongated, and permanently weaker. Concurrently, the opponent muscle undergoes contracture, functioning to take up the slack afforded by paralysis of the injected muscle, and becomes stronger (Figure 3). The toxin wears off over a period of three to four months[2]. When function returns to the injected muscle, its force is permanently reduced to allow a normal alignment of that eye relative to the fellow eye. In non-paralytic strabismus, botulinum-induced paralysis of a muscle permanently changes the ocular alignment, by both altering the length of the injected muscle and causing contracture of the antagonist muscle. In paralytic strabismus, injecting the opposite muscle helps to reduce its contracture and allows the paretic muscle to recover[13] (Figure 4).

Results of treatment

The worldwide reported experience of using botulinum toxin injections for strabismus, a procedure introduced in 1978[9], now exceeds 5,000 patients. The strabismus patients have ranged in age from three months to 90 years with a wide variety of clinical subtypes. Injections tend to yield better results for esotropias than for exotropias, and for smaller angles of strabismus (less than 15 degrees) than for larger angles. The success rates with initial treatments for esotropias range from 50 to 70 percent while those for exotropias range from 30 to 50 percent. Patients who have residual strabismus after one treatment can receive repeat injections, with correspondingly higher success rates[3,15,16].

The only side effects encountered thus far have been local in nature. Ptosis and vertical strabismus are the most frequent complications seen with botulinum toxin injections[14]. Although common (10-30%), these side effects are fortunately transient, most commonly attributed to drug diffusion to the levator and other extraocular muscles. The frequency of these complications is minimized by meticulous operator technique. Other rarer

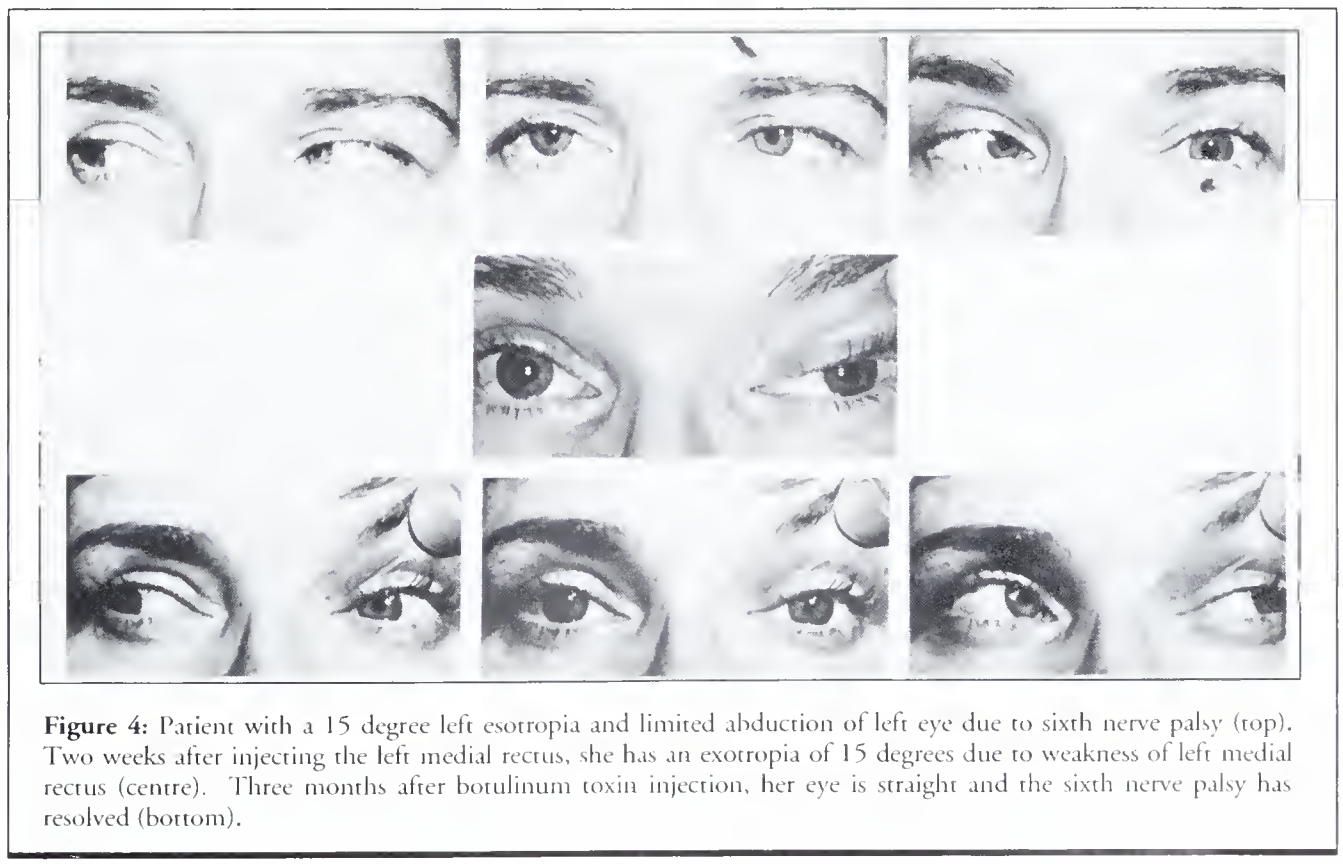


Figure 4: Patient with a 15 degree left esotropia and limited abduction of left eye due to sixth nerve palsy (top). Two weeks after injecting the left medial rectus, she has an exotropia of 15 degrees due to weakness of left medial rectus (centre). Three months after botulinum toxin injection, her eye is straight and the sixth nerve palsy has resolved (bottom).

complications include subconjunctival haemorrhage, retrobulbar haemorrhage (0.3%), and globe perforation (0.2%)[16].

The advantages of botulinum toxin injection as compared to surgery for strabismus include its brevity, minimal risks, and lack of scarring. In 15 years of use, no cases of systemic toxicity have been reported. If the botulinum treatment is ineffective, one can proceed with surgical correction. Some disadvantages of botulinum injection include (i) up to 50% of patients require more than one injection to eliminate the strabismus, (ii) the alignment changes in large angles of strabismus tend not to be as stable over the long term as with surgery, and (iii) local side effects are frequent, although transient. The drug tends to be less effective in strabismus secondary to scarring and fibrosis, such as long-standing thyroid strabismus and orbital fractures[16], where success rates are under 30 percent. Surgical interventions can yield success rates as high as 80 percent.

Facial Dystonias

Dystonia is defined as a syndrome dominated by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. The involuntary movements can vary from brief spasms to sustained contractions[17]. This discussion will be limited to the facial dystonias, the most common of which include essential blepharospasm and hemifacial spasm.

Essential blepharospasm is an involuntary disabling condition limited to the eyelids and characterized by repetitive and sustained contraction of the orbicularis oculi muscles, effectively clamping the eyes shut. It is usually bilateral, insidious in onset, and frequently accompanied by other dyskinesias[18]. The etiology of this condition is unknown but precipitating factors include bright lights, driving, stress and other anxiety-provoking situations. Patients may often adopt "sensory tricks" such as yawning, extending the neck, and wearing dark glasses to reduce or hide the disfiguring symptoms[19]. When the symptoms are incapacitating, it is not uncommon to see patients forcibly pulling their eyes open to prevent sudden closure. Some patients may become functionally blind for greater parts of the day. In the more perilous cases, sudden eyelid closure may even occur when the patient is operating a motor vehicle. Table II lists other entities that must be differentiated from essential blepharospasm.

Hemifacial spasm is a facial dystonia characterized by unilateral, intermittent contractions of the facial musculature.

Table II

Disorders Considered in the Differential Diagnosis of Blepharospasm[10]

- Ocular diseases
  - Foreign bodies, blepharitis, keratitis, conjunctivitis, uveitis, cataract, retinal diseases
- Neurological diseases
  - Basal ganglia disorders
    - Parkinson's disease, Huntington's disease
  - Gilles de la Tourette's syndrome, other tic disorders
  - Miscellaneous disorders
    - Myotonia, tetanus, tetany
- Pharmacological side effects
  - Neuroleptics (tardive dyskinesia, acute dystonia)
  - Dopamine agonists (L-Dopa)
  - Nasal decongestants (chronic use)
- Inherited reflex blepharospasm
- Psychogenic disorder (hysterical spasms)

An attack typically begins with twitching of the orbicularis oculi muscle, later progressing to involve most of the ipsilateral facial muscles. Hemifacial spasm is usually attributed to mechanical-vascular compression of the seventh cranial nerve root by a branch of the basilar artery in the cerebello-pontine angle[20]. The condition is unalterable by "sensory tricks" but is aggravated by both stress and emotion. Hemifacial spasm can rarely be caused by a tumour in the cerebello-pontine angle.

Alternative treatments for facial dystonias

Where the patient is not disabled by these conditions, no treatment is usually necessary. Treatment is indicated when there is interference with his or her daily functioning. Medical interventions have only been marginally successful in the treatment of facial dystonias, and agents used include anticholinergics, lithium, haloperidol, phenothiazines, and benzodiazepines. The side effects associated with these agents have precluded their use on a regular basis. Some cases of hemifacial spasm will respond to carbamazepine. Other treatments have included psychotherapy, hypnosis, and thermolysis of the facial nerve.

Surgical options do exist for these conditions. For essential blepharospasm, two different surgical procedures are documented in the literature: one involves a myectomy of the orbicularis muscle and adjacent eyebrow, and the other approach involves extirpation of the facial nerve and its distal fibres[21]. In the treatment of hemifacial spasm, success rates of over 90% have been reported with posterior fossa facial nerve decompression. Approximately 4% of the patients require reoperation due to inadequate decompression[21,23].

Method of Treatment

In the treatment of blepharospasm, the botulinum toxin is injected directly into both the preseptal and pretarsal portions of the orbicularis oculi muscle. If the eyebrows are also spastic, the procerus and corrugator muscles are also injected. Patients suffering from hemifacial spasm have botulinum toxin injected into the ipsilateral periocular muscles. Injections can also be made into the lower facial muscles, simultaneously weakening the perioral, perinasal, and chin musculature[17]. The dosages of toxin needed to treat facial spasms range from 20 to 50 nanograms in total, depending on the number of facial muscles involved and the severity of the spasms.

Figure 5: (a) Patient with essential blepharospasm prior to the injection of botulinum toxin. (b) After the injection, the relief lasted seventeen weeks.

Results of Treatment

Botulinum toxin was first employed to treat blepharospasm and hemifacial spasm in 1983 and was shown to be a safe and effective alternative to medications and surgery. Complete or almost complete relief of symptoms is attained in 85%-90% of serial injections for blepharospasm, and in 90% to 100% of treatments for hemifacial spasm. Botulinum toxin injections have become the treatment of choice for essential blepharospasm. The full effect of the toxin occurs within a few days and the duration of the effect can range from ten to sixteen weeks[22] (Figure 5). Thus, periodic reinjections are required in most patients on an indefinite basis.

Of all the modalities used in the treatment of hemifacial spasm, neurosurgical microvascular compression has been found to be most effective, with a reported cure rate of 88%. However, there are complications such as hearing loss, permanent facial paresis, and intracranial haemorrhage[16]. Botulinum toxin injections have been found to be equally effective in controlling the hemifacial spasm, although the relief is transient; the average duration of the relief for hemifacial spasm is four months, with a range of twelve to eighteen weeks[17,18,19].

The duration of relief after treatment is temporary for both essential blepharospasm and hemifacial spasm, and injections must be repeated at regular intervals. No systemic side effects have been reported in the treatment of either group. The most frequent side effect is ptosis, with some studies reporting an incidence of up to 25%[19]. In almost all instances, the ptosis is temporary. Up to 40% of the patients may have transient lagophthalmos, resulting in dry eyes[19]. Other rare transient complications include entropion, ectropion, epiphora, and diplopia.

Summary

Botulinum toxin injection has been used over a 15 year period in approximately 10,000 patients aged 3 months to 90 years, presenting with a wide variety of eye and eye muscle disorders. Numerous clinical studies have confirmed the safety and efficacy of botulinum toxin in bringing relief to individuals with strabismus and facial dystonias. In the treatment of strabismus, botulinum toxin injections are performed on an outpatient basis. The procedure leaves no scars and can be employed as an alternative to eye muscle surgery. Following the pioneering work in strabismus, its uses have expanded to include the treatment of essential blepharospasm and hemifacial spasm. Current clinical trials indicate that botulinum toxin may be effective in treating other neurological conditions including aberrant regeneration of the facial nerve[8], spasmodic torticollis[9], spasmodic dysphonia[10], muscle spasticity and writer's cramp[11,12].

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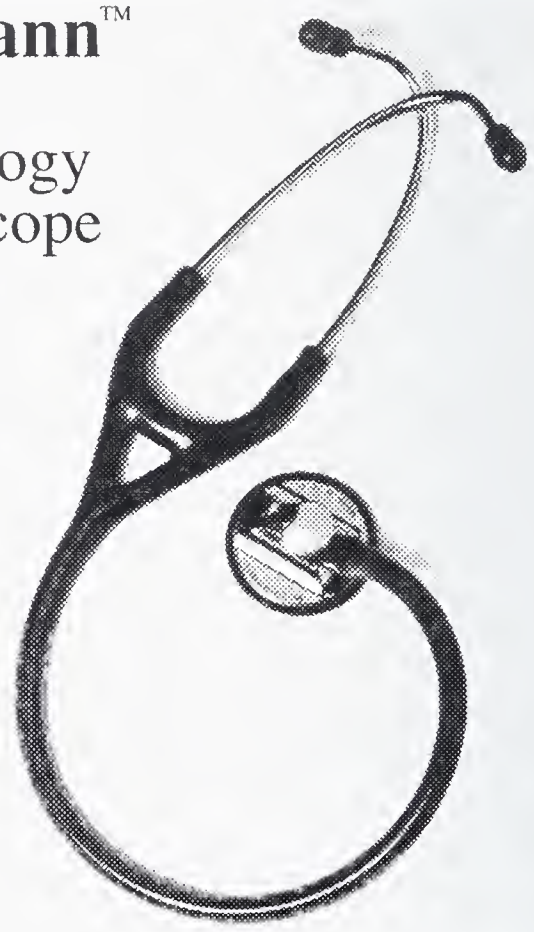

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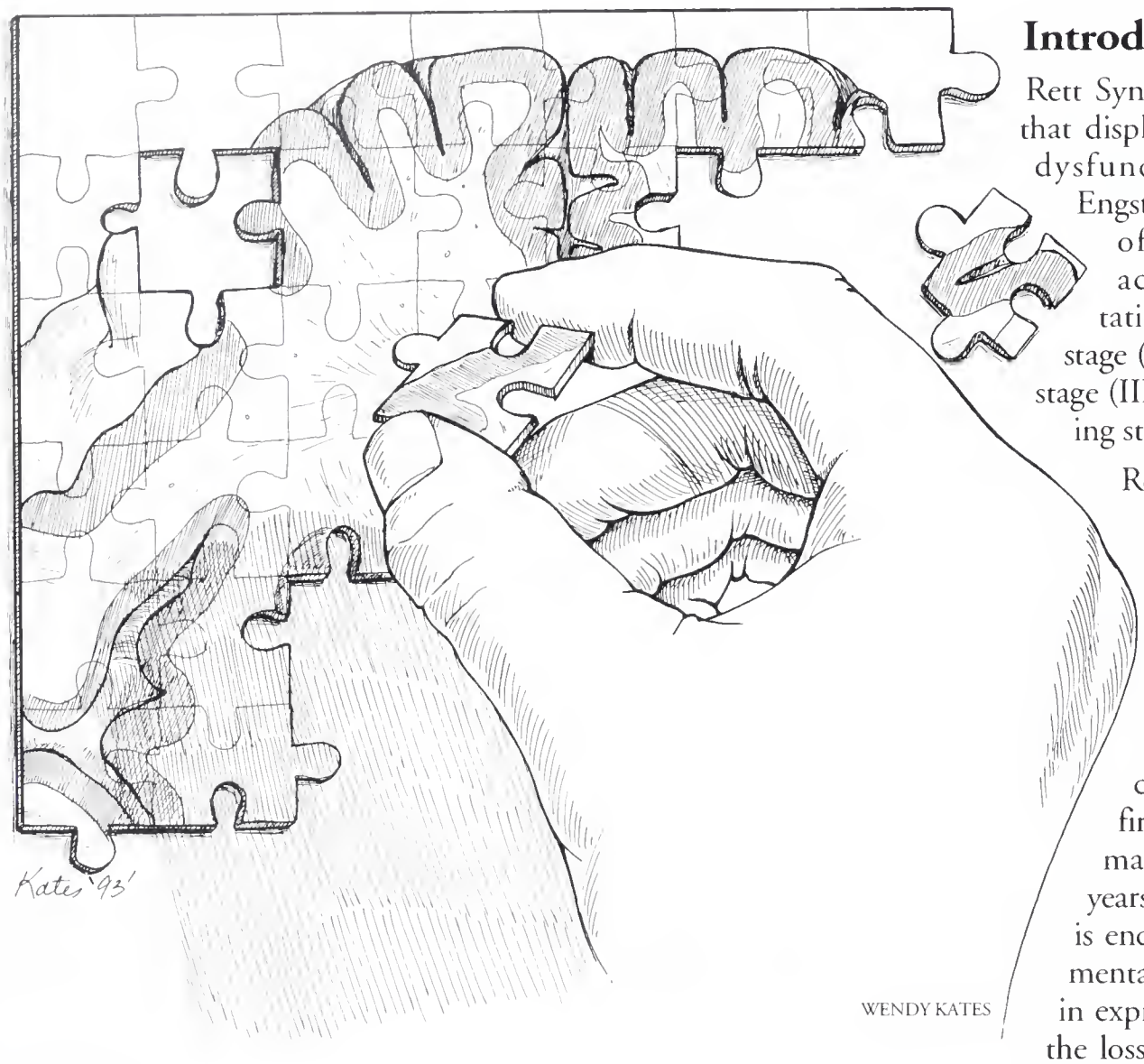


WENDY KATES

Abstract

Dr. Andres Rett first described in young girls the clinical findings of the disorder that bears his name in a German paper published in 1966. The syndrome itself remained unrecognized until 1983 when 35 cases of young females with the clinical findings described by Dr Rett were reported. Since then, efforts have been devoted to unravelling the mystery of Rett Syndrome (RS). Rett Syndrome has only been confidently diagnosed in females. Various genetic and neurochemical hypotheses have been postulated that attempt to explain the clinical and pathological findings in the Rett girls. The absence of a biological marker or abnormality has resulted in the publication of over 200 papers since 1986 that have attempted to decipher the puzzle and better comprehend the obscurity of Rett syndrome.

Introduction

Rett Syndrome is a neurological disorder that displays regressive mental and motor dysfunctions. Hagberg and Witt-Engstrom in 1986 described the course of the syndrome in four stages according to clinical manifestations[1]. These include a stagnation stage (I), a regressive stage (II), a plateau stage (III), and a slow progressively declining stage (IV) (see Table 1).

Rett Syndrome is characterized by loss of purposeful hand movements and the acquisition of stereotypical motions which include midline hand clapping, wringing, squeezing, washing, and mouthing (putting the hands in the mouth). The Rett child develops normally for the first 6 to 18 months (although some may develop normally for up to 4 years), at which time a regressive stage is encountered, presenting as developmental stagnation followed by a decline in expressive and receptive language and the loss of purposeful hand movements. Autistic manifestations (unresponsiveness, social withdrawal) usually result in an initial misdiagnosis of autism. The communication dysfunction is linked to social withdrawal. Delayed walking is often the initial concern of the parents and is attributed to the development of gait apraxia and trunkal ataxia, resulting in a gait that is wide-based and very unsteady. Unremarkable development during the first year of life makes it difficult for parents to cope with and comprehend the sudden motor, intellectual and language arrest.

Early diagnosis in the absence of the stereotypic behaviour is difficult. Due to the absence of a known biological marker, clinical findings alone must be used. Diagnosis is based on criteria for inclusion and exclusion developed in 1988 by the Rett Syndrome Criteria Work Group (see Table 2)[2]. The most striking and distinguishing clinical finding of a Rett patient is the loss of acquired purposeful

hand skills between the ages of 6 and 30 months and substitution with stereotypical midline hand wringing, clapping, or mouthing. The disappearance of purposeful, voluntary hand functions is demonstrated by the method of feeding the girls adopt: instead of reaching out for food with their hands, they reach out with their mouth. There is an eventual decrease in the frequency and intensity of the stereotypical behaviors with increasing age.

All Rett children have a normal head circumference measurement at birth but show a subsequent deceleration of head growth which has been demonstrated by quantitative MRI studies[3]. Absence of prenatal and perinatal abnormalities and a normal first year of development has complicated the search for the etiology of Rett Syndrome.

It is estimated that the prevalence of RS is 1 per 22,800 (0.44/10,000) females[4]. Only approximately 10% of the estimated 8000 to 11,000 girls with RS in the U.S. and Canada have been identified to date. Rett Syndrome is more prevalent than PKU (a condition that is screened for in all neonates in developed countries) and may be responsible for up to 1/3 of all progressive developmental disabilities in girls. What lies behind the unique stare of the Rett girls is mysterious. It is still not clear whether these girls are mentally retarded or simply in a locked in stare.

Differential Diagnosis

Rett syndrome is often confused with infantile autism. Although the two syndromes have many similar characteristics, they are distinguished by the fact that autism involves a regression of verbal, behavioural and relational skills, while RS involves a regression of motor, verbal and cognitive skills. Disorders of lysosomal and mitochondrial enzymes, disorders of pyruvate metabolism and storage diseases also present as regressive motor and mental syndromes (see Figure 1)[5]. The differential diagnosis of infants with mental regression and motor disturbances may also include other progressive encephalopathies and psychiatric disturbances. Angelman ("happy puppet") Syndrome and Prader Willi Syndrome are two disorders that involve chromosome 15 mutations and because of the regressive course of these syndromes may be confused with RS.

Table 1

Staging System Describing the Progression of Rett Syndrome[2]

Stage 1 **Onset: 6-18 months** **Duration: months**	**Stage 3** **Onset: 2-10 years** **Duration: months to years**
Developmental stagnation Deceleration of head circumference Hypotonia Disinterest in social activities EEG - normal Loss of purposeful hand movements	Severe mental retardation Seizures Ataxia Apraxia Scoliosis Bruxism Breathing dysfunction EEG - generalized slowing, disappearance of posterior rhythm
Stage 2 **Onset: 1-3 years** **Duration: months**	**Stage 4** **Onset: >10 years** **Duration: years**
Rapid developmental regression Irritability Hand wringing/clapping/tapping/mouthing Loss of expressive language Autistic behaviour Seizures EEG - slow background; focal or multifocal spike and wave	Muscle wasting Progressive scoliosis Decreased mobility Absence of expressive/receptive language Reduced seizure frequency

Neuropathology

Autopsies have been performed on several RS girls, with various neuropathological abnormalities noted. However, the clinical correlates to these neuropathological anomalies cannot be delineated[6,7]. The abnormalities include:

1. Diffuse and *progressive* reduction in brain size by 14-34%. One of the inclusion criteria for the diagnosis of RS is a deviation from normal head circumference growth, which is consistent with a reduction in brain size. Whether this deviation from normal brain growth is a result of the syn-

Table 2

Diagnostic Criteria for Rett Syndrome

Necessary Criteria
1. Normal prenatal and perinatal period.
2. Normal head circumference at birth.
3. Normal psychomotor development until 6 months.*
4. Loss of purposeful hand skills (6-30 months).
5. Stereotypic hand movements such as hand wringing/squeezing/clapping/tapping/ mouthing replacing purposeful hand movements.
6. Deceleration of head growth (between 5-48 months).
7. Gait apraxia and trunkal apraxia/ataxia appearing between 1 and 4 years.
8. Appearance of psychomotor retardation.
9. Severly impaired expressive and receptive language.
10. Communication dysfunction and social withdrawal.
11. Diagnosis not conclusive until 4 to 5 years of age.

*Normal psychomotor development has been reported for some Rett girls in the first 4 years. The average normal developmental period prior to regression is 10 months.

Supportive Criteria
1. EEG abnormalities: - epileptiform discharges with or without clinical features
   - slow walking background
2. Seizures
3. Scoliosis
4. Spasticity
5. Breathing dysfunction: -intermittent hyperventilation
   -breath holding spells
   -periodic apnea
   -forced exptulsion of air or saliva
6. Peripheral vasomotor disturbances
7. Growth retardation

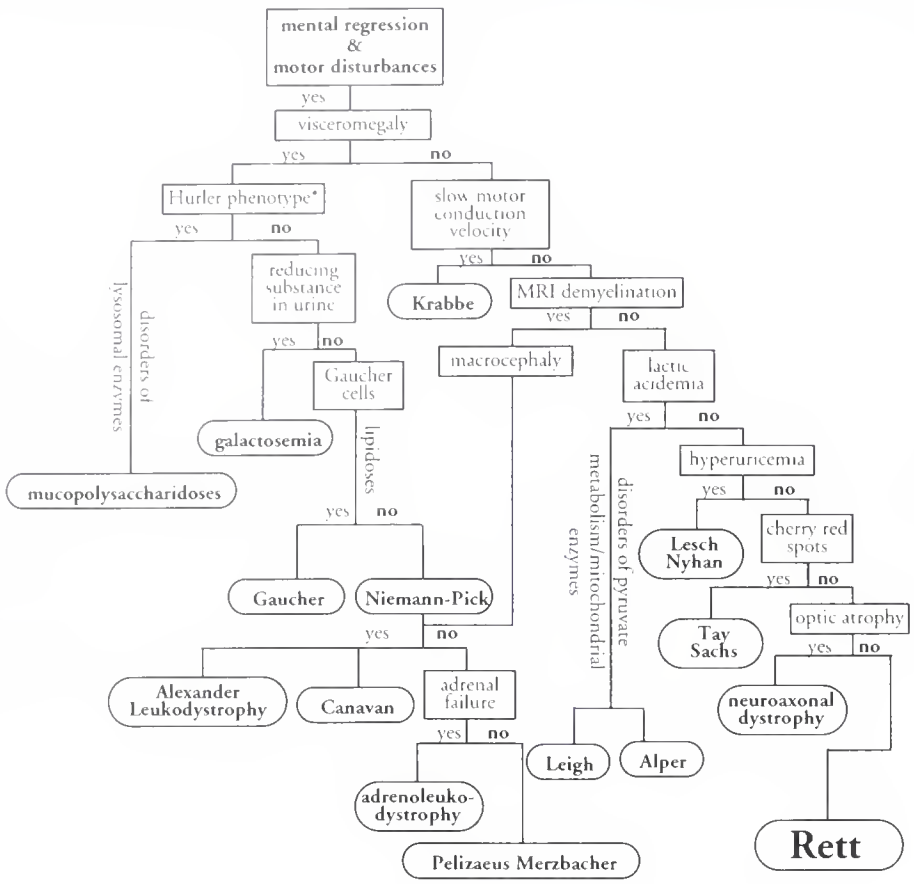
Exclusion Criteria
1. Organomegaly or signs of storage disease.
2. Microcephaly at birth.
3. Retinopathy or optic atrophy.
4. Intrauterine growth retardation or perinatally acquired brain damage.
5. Evidence of other metabolic or progressive neurological disorder(s)*
6. Acquired neurological deficit resulting from head trauma/infection.

*see Fig. 1

(Adapted from Hagberg et al. 1988)

Figure 1

DDx for Infants With Mental Regression and Motor Disturbances



*abdominal hernia, coarse facial features, corneal opacity, deafness, mental retardation, stiff joints, visceromegaly

(Adapted from Fenichel 1988.[5])

drome or whether it represents the etiology has not yet been determined. Growth factors, dysgenesis and synaptic abnormalities may be responsible.

2. Hypopigmentation of the zona compacta of the substantia nigra without loss of nigral neurons. The zona compacta has been implicated in Parkinson's Disease and it has been suggested that Rett Syndrome shares similarities with Parkinson's.

3. Mild vacuolation of the myelin in various white matter regions of the CNS.

4. Increased amounts of neuronal lipofuscin (pigment granules representing lipid-containing residues of lysosomal digestion).

5. Greatly compressed cortical layers.

6. A one-third decrease in neuronal size.

7. Reduction in the size of the Purkinje cells of the cerebellum.

8. Decrease in both dendritic length and branching in all areas, which is suggestive of a synaptic abnormality.

The functional significance of these lesions remains unexplained. There is no decrease in the cell population (neuronal growth arrest, rather than degeneration occurs) and there are no other gross developmental or maturational abnormalities seen by histochemical techniques.

Genetics

The Rett phenotype is exclusive to females. The majority of cases are thought to result from spontaneous mutation. Two percent of RS patients show a familial relationship. Thirteen familial cases are known worldwide. Patterns of inheritance in these families suggest a genetic mechanism. Within these families are:

1. A mother and daughter with RS (the only known example of vertical transmission)[8].

2. Two sisters with RS[9].

3. Four cases of concordance in monozygotic twins.

4. Two half sisters with RS (same mother).

5. Occurrence only in females.

An X-linked dominant mutation lethal in males has been proposed, with transmission by females who produce affected daughters, normal daughters and normal sons in equal proportion. The mutation is thought to be on the X chromosome since only female cases have been reported, with the male fetus aborting and the female being able to compensate with one normal X chromosome[10]. Approximately 60% of the X chromosome has been studied in familial cases with no evidence of abnormality. This allows for the exclusion of the segments studied but investigation is still required of the distal portions of the X chromosome.

Metabolic interference, a non-Mendelian mechanism, has also been proposed as a possible genetic abnormality. A metabolite produced by an abnormal gene or a defective lysosome or mitochondrion may interfere with normal brain development. Since a mitochondrial abnormality has not been found, other molecular or genetic mechanisms producing a yet unidentified toxic metabolite may potentially be involved.

A disturbance in X-inactivation has also been postulated[11]. In the cells of the female, only one X chromosome is active; the second is a condensed X chromosome whose genes are inactive (with a few exceptions) and which appears as the sex chromatin. Inactivation occurs during embryonic life. This inactive X chromosome replicates its DNA very late in the S-phase of the cell cycle, thus it is referred to as the late replication X chromosome. It is possible that a disruption of the timing of the replication of one or more genes on the late replicating X chromosome could disturb the inactivation. These genes may then remain active for part of the cell cycle, increasing the gene dosage which may interfere with normal brain development.

A mutation in the X chromosome has not been found to date and all other genetically based proposals have not yet been proven. A recent genealogical study from Sweden[12] traced RS families back 7-10 generations. Of the 8000 ancestors that were studied, 49% came from 9 small rural areas and 42% of these came from the same farm or group of houses. This study, along with the reported familial cases, is supportive of a genetic transmission. The mode of transmission is still not clear.

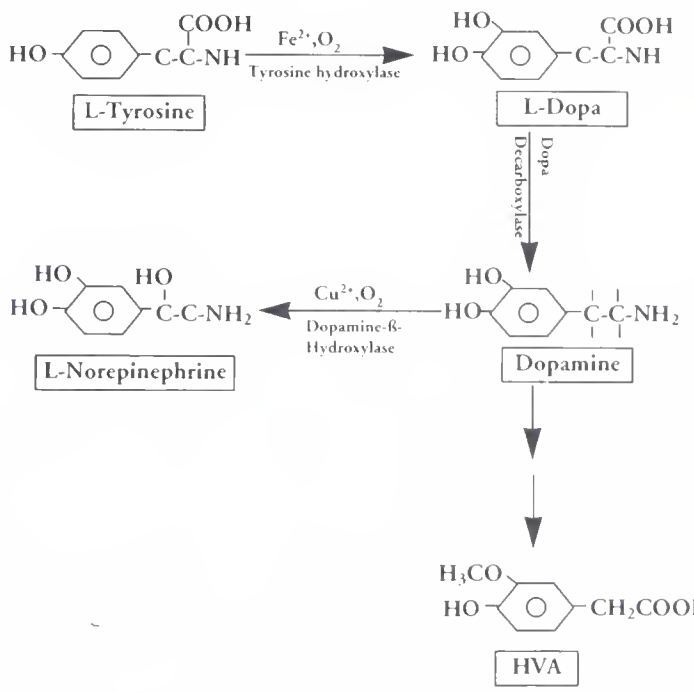
Neurochemistry

Analysis of cerebrospinal fluid and other neurochemical studies have produced conflicting and sometimes non-reproducible results. A neurochemical abnormality remains unproven although many plausible hypotheses have been proposed.

The dopamine system has been suggested to be responsible for the extra-pyramidal dysfunction found in Rett girls. Decreased levels of biogenic amine metabolites, including HVA, in the CSF (see Figure 2) have led to the speculation that post-synaptic supersensitivity caused by decreased dopamine activity leads to a hyperactive dopamine system[7,13].

Post-mortem neuropathological findings of hypopigmentation in the substantia nigra are also consistent with a decreased dopamine (DA) synthesis. Neuromelanin in the substantia nigra is a polymer of DA and thus the degree of pigmentation is proportional to the amount of DA available. Hypopigmentation thus correlates with decreased DA synthesis.

Figure 2:
Conversion of L-Tyrosine to DA and Norepinephrine



(Adapted from Pelligra et al.[15])

Positron emission tomography (PET) has shown D_2 dopamine receptor binding to be in the low to normal range and this conflicts with a proposed hyperactive dopamine system. Other studies have failed to show a reduction in dopamine and epinephrine metabolites in the CSF[14]. These conflicting studies have failed to elucidate the role of dopamine in the pathogenesis of Rett Syndrome.

Cycles of hyperventilation (resulting in hypocapnia) alternating with periods of apnea are a breathing abnormality present at some time in almost every case of RS. This breathing disturbance has recently been linked to neurotransmitter dysfunction in RS[15]. Abnormal respiratory function causes chronic cerebral hypoxia and hypocapnia which may be responsible for impaired biogenic amine production. Hypocapnia results in an increased affinity of hemoglobin for O_2 (Bohr effect) and further deprivation of oxygen at the brain tissues. Abnormal tissue oxygen metabolism is known to cause a reduction in biogenic amine synthesis. The conversion of L-tyrosine to L-dopa is rate limiting and dependent upon O_2. The fact that stereotypic signs and symptoms are worsened by increased effort and relieved during sleep (when brain O_2 consumption is unchanged, but cerebral blood flow increases, making more O_2 available) strengthens the hypothesis that a decrease in dopamine, leading to a hyperactive dopamine system, may be responsible for the findings in Rett Syndrome.

A mitochondrial abnormality was initially suspected due to findings of abnormal pyruvate and lactate levels in some patients. Mitochondria produce ATP and the main consumers of ATP are the brain and muscles. Deficiency of ATP due to a mitochondrial abnormality is likely to affect these organs and could induce the mental and motor disturbances seen in RS. The presence of only one reported mitochondrial defect in muscle[16], inconsistent pyruvate and lactate levels, and the inability of this hypothesis to account for the occurrence only in females, have resulted in the rejection of this proposal.

Lipid neurochemistry has also been analyzed[17]. Gangliosides, cerebrosides and phosphoglycerides were found to be at normal levels. Reduced ganglioside content and distributional abnormalities of the complex gangliosides GD1a and GT1b in the cerebellum of one patient has raised suspicions of a synaptic abnormality. Complex gangliosides are associated with synaptic membranes and an abnormal or hindered biosynthesis of these complex gangliosides may be responsible for aberrant development of the synaptic connections.

Hagberg et al. reported high levels of glutamate in the CSF of RS patients[18]. Glutamate, an excitatory neurotransmitter, has been shown to have neurotoxic and neurodegenerative properties at high concentrations. It is suspected that high glutamate levels may be responsible for the neurodegenerative course of RS.

Three studies found an increase in CSF ß-endorphin, an endogenous opioid, in 89% of 71 girls with Rett Syndrome involved in the studies[19]. This conflicts with a report[7] that showed a decrease in ß-endorphin levels in 5 RS subjects. Opioids have been implicated in pain modulation, respiration, appetite, endocrine function,

temperature regulation, motor activity, sleep, learning, and memory. Administrations of ß-endorphins in animal studies have resulted in the development of RS-like symptoms: loss of voluntary grasping, hyperventilation, respiratory depression, body and limb jerks, seizures, and decreased intestinal motility. Trials with naltrexone[19], an opioid antagonist, have shown some amelioration of the RS features, but preliminary results have been disappointing. Future trials may implicate ß-endorphin in RS, but its involvement is still unproven.

Neuroimaging

Quantitative MR analyses have revealed global hypoplasia and atrophy of the brain, although qualitative analyses reveal no abnormalities[3]. The most significant findings include progressive cerebellar atrophy with increasing age. Cerebellar atrophy may help to explain some of the motor deterioration seen in Rett girls. The cerebellar width, fourth ventricle and pituitary gland were found to be significantly smaller in patients with Rett Syndrome in comparison to control subjects[3]. The cerebrum and basal ganglia were also found to be significantly smaller. Poor nutrition and seizures may be responsible for these anomalies, or the disease itself may be the reason for this widespread brain hypoplasia.

PET studies using ^{18}fluorodeoxyglucose, a radioactive glucose analog, revealed hypometabolism in the occipital cortex and hypermetabolism in the frontal cortex[20]. PET examinations studying O_2 metabolism and cerebral blood flow (CBF) on 6 RS patients showed CBF to be within normal limits in all patients while cerebral rates of O_2 metabolism were low for 5 of 6 patients[20]. However, all patients had a lower O_2 metabolism in the frontal than in the temporal cortex and the ratio of the frontal to temporal CBF was below normal. This is suggestive of a loss of hyperfrontality[21]. Hyperfrontality normally appears between 1 and 2 years of age, the same time period that RS regression appears, and is thought to be associated with the development of higher cortical function. This loss of hyperfrontality is thought to be due to a disturbance in the dopaminergic projections to the frontal cortex. A decrease in CBF and frontal to occipital O_2 metabolism may be due to a decreased dopamine input to the frontal cortex.

Electroencephalographic Studies

70-80% of RS girls develop seizures. At present there is no "typical" EEG finding, but abnormal cortical electrical activity is present in most RS girls[22]. These may include:

1. Rhythmical slow background activity (3-5 Hz) (67%)
2. Abnormal sleep patterns (50%)
3. Slow spike-wave complexes (20%)
4. Spikes or sharp waves (multifocal), enhanced by sleep.
5. Declining EEG abnormalities with increasing age.

The EEG abnormalities do not appear until 2 years of age. Discharges (sharp waves or spikes) are a common feature of RS and are not related to the onset of seizures. In younger patients, there appears to be a relationship between stereotypic movements and EEG features[23]. Tactile stimulation of the hands evokes a sharp wave over the contralateral somatosensory area in some girls.

Management and Treatment of RS

While various therapeutic approaches do nothing to alter the course of the disease, they are helpful in improving mobility, preventing deformities and ameliorating the stereotypical behaviors of the RS child.

Music Therapy

Music therapy has been shown to result in a temporary cessation of the stereotypical RS movements (e.g. hand movements, teeth grinding)[24]. It is believed that perception of music is regulated and controlled by a primitive region of the brain and thus it is not surprising that severely retarded children, who most commonly have a higher cortical lesion, respond to music. It is still not clear whether the RS girls are retarded or "locked in" by a movement disorder.

Hydrotherapy

Movement in water is used to improve the range of motion in children with motor difficulties. Some RS girls lose their ability to walk and are confined to a wheelchair, making their management more difficult. Hydrotherapy is used to improve strength and range of motion and is one of the ways of maintaining ambulation in RS girls. Ambulation is a critical skill that must be developed or maintained in RS girls in order to make their management less complicated.

Orthopedics[25,26]

Orthopedic intervention may be necessary to correct any foot abnormalities so that RS girls can maintain and develop independent standing and ambulation. 64% of patients with RS develop an orthopedic problem. Scoliosis (a lateral curvature of the spine) is the most frequently observed orthopedic problem in RS girls. The scoliosis is progressive and thus early bracing is used to delay the progression. Spinal fusion may be implemented in non-responsive cases. The scoliosis results from an imbalance in the muscle tone around the curvature.

Electric stimulation is currently being tried on RS girls as a method to try to control muscle tone and decrease the frequency of the repetitive stereotypical behaviour.

Coxa valga (alteration of the angle made by the axis of the femoral neck and the axis of the femoral shaft), kyphosis, and contractures (permanent muscle contraction due to tonic spasm or fibrosis) are other orthopedic

manifestations commonly found in RS. Bracing and surgery are indicated to prevent or correct the deformity and, most importantly, to maintain ambulation[25].

Splinting has been attempted to try to control or stop the stereotypically repetitive hand wringing and clapping movements of the RS girls. These attempts have been ineffective in improving attention and decreasing the intensity and frequency of the stereotypic hand movements[26].

Physical Therapy

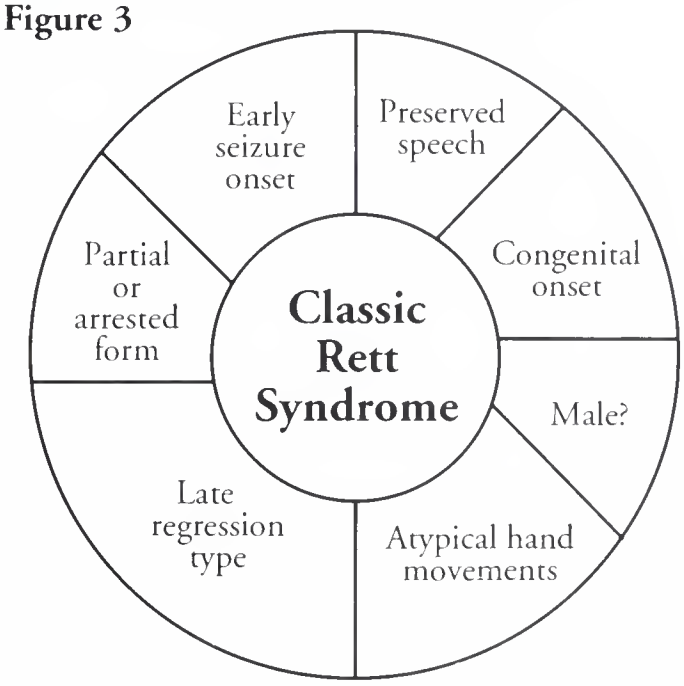
Physical therapists play an important role in the management of the RS child. Ball therapy, body rotation and weight shifting exercises are some approaches used to improve the apraxia and ataxia.

Dietary Counselling

Some Rett girls lose weight as they grow older. This may be due to the loss of the ability to communicate and self-feed. Poor nutrition has been correlated with the stereotypic behavior. A high fat ketogenic diet and an adequate caloric intake have been shown by Haas et al. to improve the stereotypic behavior and seizure control of the Rett child[27]. These authors postulated a defective carbohydrate metabolism in Rett girls based on their findings of elevated CSF pyruvate and thus introduced fat as an alternative source of energy.

Atypical Presentation of Rett Syndrome

Figure 3



(Adapted from Hagberg et al. 1993[28])

Constipation is another common diet-related problem. Failure to consume fibre and high fluid-containing foods may be responsible for the constipation and alteration of the diet has been very helpful in maintaining regularity. Irritability, aggressive behavior such as hitting others, and screaming cries that occur without an apparent reason, may be due to the constipation-induced abdominal pain.

RS girls may also show some self-injurious behavior. The most common of these is scratching. Whether this scratching is a behavioural manifestation or indeed has a nonpsychiatric cause is unclear.

Atypical Rett Syndrome

Although presentations generally follow the classical picture as defined by the diagnostic criteria, some variability does exist in the presentation of Rett syndrome[28] (see Figure 3). Some RS girls have been reported to possess a relatively advanced communication ability with preserved speech (2-3 words) indicating retention of some degree of intellectual capacity[29]. Some RS girls may not show signs of significant regression until after two years of age. Even though the mean age of regression occurs at 10 months, there have been literature reports of girls that develop normally for up to four years, only then to regress dramatically and attain the RS features and stereotypes.

Although a large number of RS girls lose their ability to walk , a significant number will still maintain the ability to ambulate, even at a relatively advanced age (>20 years).

The majority of Rett girls develop a characteristic repetitive and unchanging midline hand movement. Although there is a remarkable similarity in the character of these hand movements from one Rett girl to the other, some girls develop atypical hand movements that may involve predominantly one hand or may be associated with a symmetric tapping of a body part (e.g. the head).

Some patients present with early onset of seizures and may as a result show early and rapid regression[30]. In addition, there are reports of some girls that satisfy all RS diagnostic criteria except for an initial normal period of psychomotor development or purposeful hand use. Although these individuals did have an early developmental delay, they continued to regress in the first year of life. Whether these girls developed normally for an atypically shorter period of time (<3 months) is difficult to ascertain. Goutieres et al.[30] reported one child that was abnormal from birth and did not show further deterioration. She went on to develop the classic Rett syndrome behaviours and stereotypes.

Boys with Rett-like features have been reported in the literature. Eeg-Olofsson et al. reported one 13 year old boy who met the majority of the necessary criteria and most of the supportive criteria for the Rett Syndrome[31]. He was found to have a mitochondrial abnormality, an anomaly not considered part of the etiology of Rett Syndrome. Philippart reported 2 males in their late thirties that presented with the clinical findings of RS[32]. Both had a normal early development and a regression that led to hand wringing. However, both patients showed a normal head circumference with no evidence of atrophy. Because their developmental regression is difficult to substantiate, their Rett Syndrome presentation has been questioned. Even though these questionable atypical male Rett patients have been documented, only females have been found to meet all of the necessary criteria for a diagnosis of Rett Syndrome.

Pharmacotherapy: Trials with Bromocriptine

Bromocriptine is a dopamine agonist that has been used with some success in treating RS girls. A recent report from South Africa revealed a marked improvement in motor ability (walking short distances without support, holding objects for a few seconds in the hands), cessation of hyperventilation, decreased frequency of bruxism, and reduction in stereotypic hand movements in two girls who were put on a daily dose of bromocriptine[33]. The girls were also noted to be more alert and receptive and started to utter 2 to 3 meaningful words.

Zapella et al. treated 13 Rett girls with bromocriptine[34]. 4 began to utter a few words, 5 had reduced frequency of hand stereotypies, 3 had reduced episodes of bruxism, 3 had motor improvements and 8 were more alert and responsive.

The dopaminergic system has been hypothesized to be responsible for the manifestation of RS. Whether bromocriptine acts to stimulate the dopaminergic system directly or indirectly by causing a supersensitization of the receptors, or desensitizes the receptors causing a decreased dopaminergic activity has not been well explored. Further trials involving a larger RS population are required in order to study the therapeutic possibilities of bromocriptine.

Conclusion

The intense, passionate and unmistakable stare of the Rett girls is as unique as the syndrome itself. Even though a great deal of effort and time has been put forth to try to unravel the mystery of Rett Syndrome, many questions still remain unanswered. The search for a better understanding and correlation of the clinical peculiarities with the neurochemical, genetic, and pathological findings continues. Is the cause a genetic factor resulting in an age-specific deficiency? Is a slow viral infection plausible? Could the arrested brain development be explained by some deficient growth factor or biosynthetic component? Could a neurochemical abnormality (ß-endorphins, neurotransmitters) account for the clinical findings in RS? Is a Rett male a clinical variant or is the syndrome lethal in males?

Since RS does not present with a continuing regression, a developmental arrest is most probable. Recent studies suggest that a genetic cause is most likely, although a primary or secondary neurochemical abnormality has not been ruled out. RS could be multifactorial.

The RS girls may have more intact cognition than is recognized. Their capability for reception, processing and integration of information is not clear. We still are unable to explain the motor and mental regression and cannot find a biological marker that allows for clinical diagnosis. With an increasing number of new patients being diagnosed with Rett Syndrome, the cause of Rett Syndrome is being sought after by many investigators and interest in the syndrome is vastly increasing. The etiology of Rett syndrome may give us insight into other degenerative diseases such as Parkinson's and Huntington's diseases and a better understanding of motor disorders such as Tourette Syndrome. The search for the missing pieces of the puzzle is challenging and the answer to the Rett mystery may eventually allow us to determine what lies behind the secret mind of Rett girls.

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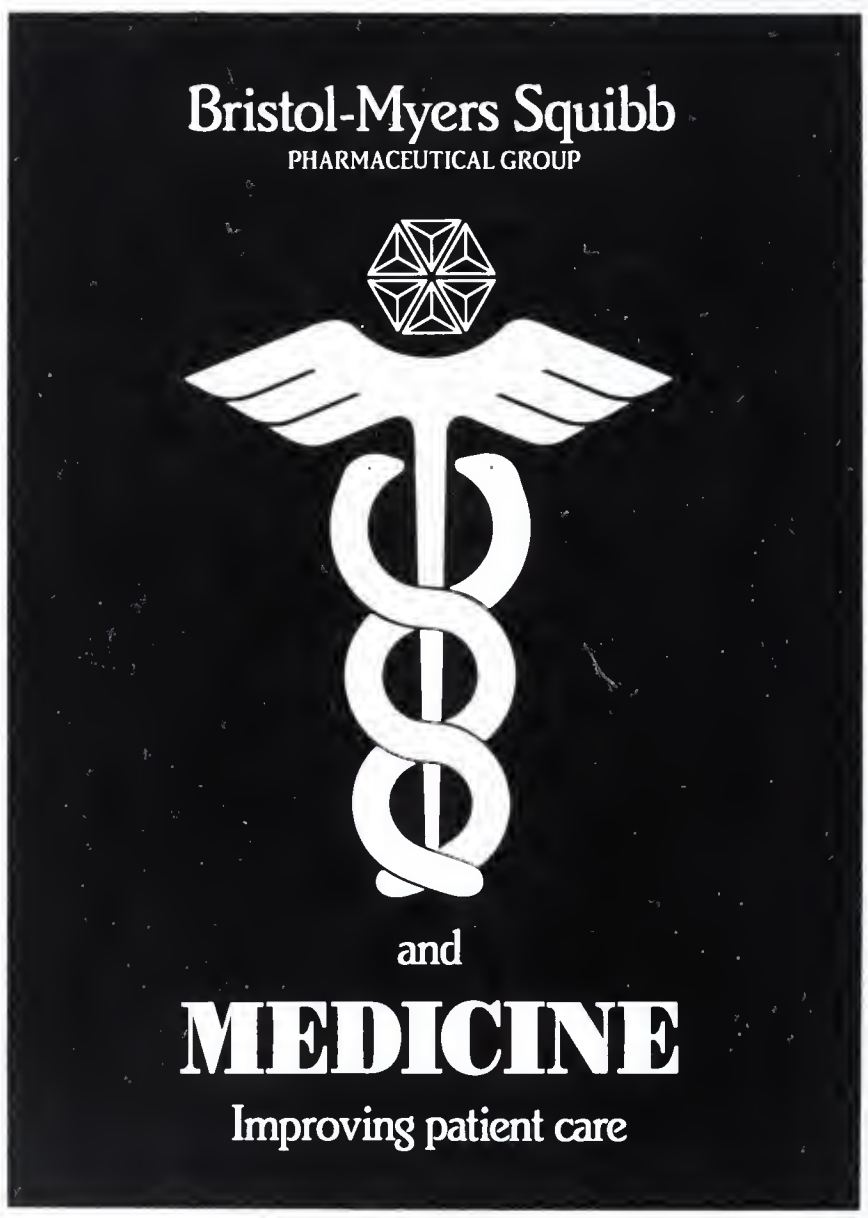

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Sexual Assault and the Role of the Physician in the Healing Process

M. Laura Hopkins, B.Sc. (Hon), M.Sc. (9T5)

PAULETTE DENNIS

Abstract

Physicians learn during their hospital-based training about the protocol for the history and physical examination of a sexual assault victim and the manner in which evidence is collected for the Sexual Assault Evidence Kit (SAEK). While this information is important for a criminal investigation, the psychological implications of sexual assault are often not fully appreciated by physicians. Crisis intervention which is intended to help restore women to their pre-assault level of functioning must focus on the process of adapting to and coping with the fear, anger, depression and other emotions known as "Rape Trauma Syndrome". A clear understanding of this process makes it a useful diagnostic tool since an accurate assessment of where the victim is in the Rape Trauma Syndrome will enable physicians to respond appropriately to the needs of victims. The objective of this paper is to describe the Rape Trauma Syndrome so that physicians and physicians-in-training may gain a more complete appreciation of the impact of sexual assault on health. Moreover, the paper aims to teach medical professionals about their role in the healing process and hopefully diminish the uneasiness that accompanies treating women who have been assaulted.

Definition and Incidence

Sexual assault is a crime in our society. Legally defined, it is "an act of force in circumstances of sexuality" and involves the use of physical force, threat and intimidation[1]. In our society, approximately 99 per cent of all sexual assaults are committed by men against women[2]. Accordingly, the focus of this paper is on women victims of sexual assault.

Sexual assault is common; it has been reported that 27 per cent of Canadian women will suffer a rape or other sexual assault during their lifetime[3]. Given that police officials state that only about 1 in 10 sexual assaults are reported, it is likely that this figure underestimates the true incidence of sexual assault[4] .

Rape Trauma Syndrome

Victims are either attacked by someone whom they have trusted or are the subject of a "blitz" attack by a stranger. Most of us associate sexual assault with the latter case but it is known that the majority of women (68.5 to 83 per cent) are sexually assaulted by men they know[3,4]. Because of the variability in the conditions of sexual assault, diversity exists in women's subsequent reactions. Observation and research have shown, however, that the 'Rape Trauma Syndrome' is common to the majority of survivors[5]. The syndrome was first described by Burgess and Holmstrom[5] in the 1970's after they interviewed more than 600 survivors of sexual assault. It is composed of two parts: the "Acute Phase," which may last for up to several weeks after the assault, and the "Reorganization Phase" which merges with the first but continues for months or even years afterward. Physicians who are aware of the Rape Trauma Syndrome and the processes involved can better understand what women are experiencing, help support and validate their feelings, and become an active part of the healing process.

The Acute Phase: Immediate Impact Reaction

Emergency doctors are likely to be the first physicians to encounter women who present immediately after an assault. Given the nature of the physical and emotional assault which has just taken place, most physicians would probably expect to see a very distraught, dishevelled and hysterical individual in the examining room. While it is true that this may in fact be the case for some, it is equally possible that the physician may encounter someone who appears very much in control of her feelings and is outwardly calm. These are known respectively as the "Expressed" and "Controlled" styles. The most serious mistake that a physician can make with a woman who exhibits the latter behaviour is to underestimate the degree of trauma. Indeed, all victims of sexual assault have been held captive by force and this carries with it, however subtly, the threat of death. The impact of being so dehumanized by another person and the amount of terror that has just been experienced have long-lasting effects. Physicians must remember, *always,* to see beyond the outer façade and to realize the important effect that their behaviour (gestures, words, and tone) will have on the victim.

Providing good medical care and medical substantiation for the victim's story are among the physician's immediate responsibilities to the victim. Physicians are also in a unique position to initiate the emotional rehabilitation of the victim by offering psychological support[6]. Reassurance concerning her safety and acknowledgement of the fact that she has managed to survive a life-threatening assault is a positive starting point to the process of recovery. Physicians should ask the victim if she would like to make a phone call to ask a family member or friend to come to the hospital for immediate support. Ideally, a rape crisis counsellor or other specially trained individual will be available to stay with the victim throughout the examination. Since the behaviour and attitudes of the hospital staff are frequently taken by the victim as indicators of the kind of reception she can expect from others, the victim's experience at the hospital will affect her subsequent decisions about seeking further professional help. A physician who expedites the victim's care and treats her with sensitivity and respect may, therefore, increase the victim's confidence that she will be treated sensitively by others. Without a doubt, this may ultimately determine whether or not a victim will report the assault to police.

For many sexual assault victims, the most important immediate issue is regaining a sense of control. Allowing the victim to make decisions about her treatment and keeping her informed about all aspects of her care can help in this respect. She needs to be offered choices, to be asked what she would like to or needs to do, and to have those choices respected. Victims may also be feeling a loss of control over their emotions. One of the ways in which a physician can help is to let the victim know that it is normal to experience a wide range of emotions following an assault, including depression, embarrassment, guilt, anger and vulnerability[7]. If the victim has some idea of what to expect, it will ultimately increase her sense of control over her situation.

The Acute Phase: Examination and Treatment

The physical examination may be an especially uncomfortable experience for the sexual assault victim. It is possible that a word or action (i.e. touch) may trigger a flashback that is accompanied by an emotional outburst. In particular, it is quite conceivable that the gynecologic examination might seem like a repeat assault. She may tense or start to sob; if this happens, the physician should show sensitivity to her needs by stopping the examination and waiting for her permission to continue. It is important to respect and accept these responses and encourage her if she wants to talk. The more sensitive and gentle the physician, the more likely it is that a victim will be reassured about her health[8].

At any time during the interview and physical, the victim may ask questions about the possibility of pregnancy or sexually-transmitted diseases. Indeed, these questions may be the sole reason that the victim seeks medical attention and they should be answered clearly and accurately. As much time must be taken as is necessary for discussion of issues of concern to the victim and this offers another opportunity to reassure her about her physical well-being. It is important for the physician not to become distracted or interrupted during the interview. Leaving a victim in the middle of an interview or physical, regardless of circumstances, implies her emotional and physical injury are not important enough to merit the doctor's undivided attention. This would contribute to a feeling of low self-worth in the victim. Before the victim leaves the hospital, arrangements should be made for a follow-up visit, ideally

with a rape crisis counsellor or specially trained social worker. In communities where highly trained counsellors are not available, an appointment should be made with a family physician or another professional who can build a rapport with the victim over the long-term.

The Acute Phase: Delayed Impact Reaction

A victim's feelings of fear and stress do not end when the assailant leaves the scene of the assault, nor does it end when she leaves the hospital. Similarly, the physician's role in the healing process does not end when the victim leaves the hospital. The victim will continue to experience a variety of intense emotions. It may be useful to reassure her once again that these feelings are normal and to encourage her to identify strengths and employ previous coping strategies. Offering to help her obtain more information about her medical situation or about police involvement can further serve to reduce anxiety.

Problems may arise in the victim's relationships with close personal contacts including her spouse or partner, family and friends. It is possible that these contacts may feel angry and upset that they couldn't somehow prevent the assault. It is also possible that such individuals may be blaming her for the assault. They may offer statements like, "What were you doing out walking by yourself at 10:30 PM?" Critical comments of this nature have disastrous effects on the victim's self-image and there is a possibility that she has already entertained similar thoughts herself. The physician can help the victim recognize these thoughts as being false and reassure her that the assault was *not her fault.* It may be helpful if the physician offers to meet with close contacts and listen to their concerns since this may help them become more supportive. Ideally, the physician could assist in bringing about changes in the responses of people to the victim and also help her take a more active role in her own recovery. The desired outcome is a woman who feels less isolated and less helpless.

The Acute Phase: Special Issues

During the Acute Phase there may also be important issues relating to the victim's physical well-being such as gastrointestinal irritability, insomnia, fatigue, genito-urinary problems, muscle/soft tissue tenderness, tension headaches and nausea[9]. These medical and psychosocial issues are numerous and often are interconnected. A physician who fails to appreciate this and subsequently neglects some of these issues will not likely promote long-term healing. Studies have shown that unresolved issues can resurface years after trauma occurs and cause physical and psychological problems[10,11]. For instance, statistics collected over a six month period in 1990 at the Jean Tweed Substance Treatment Center for Women found that 60 per cent of clients were victims of sexual assault. In addition, a Canadian study of psychiatrically institutionalized women found that 37.8 per cent of those sampled had been sexually assaulted[12].

The Reorganization Phase: The Long - Term Process and Remote Presentation

The process of healing continues for the victim in the "Reorganization Phase". This second phase begins when the woman starts to reorganize her lifestyle in a way that is acceptable to her, given the assault experience. She may move, change her phone number, or even change her job in order to avoid the possibility of being reminded of the assault. Her employer may resemble her assailant, or she may be afraid to stay in her home if this is where the assault occurred. These changes are made in the interest of self-preservation but may also represent the response to a phobia which has developed as a reaction to the assault. Sleeping difficulties may persist along with nightmares involving circumstances of the assault. The victim may also be experiencing some degree of sexual dysfunction at this time. It is during this phase of recovery, months after the assault, that most victims of sexual assault will present to their family doctor or gynaecologist[10]. Women may present with complaints such as sleep disturbances, depression, anxiety and/or sexual problems. The origin of such complaints will remain a mystery to physicians who do not probe for underlying causes of the conditions they treat. Physicians could do much to help victims of sexual assault if they incorporated screening for sexual assault into their history-taking. Asking women if they have ever been sexually assaulted lets them know that they can talk to someone about the trauma. However, physicians are not expected to be able to counsel victims. In fact, without special training in the counselling of sexual assault victims, a physician might actually do harm despite well-meaning intentions. It is enough to listen, to let her know that she is not alone, and to advise her of the support services available to her. A physician should be aware of the services that are available in the community and should have this information on hand in the office so that a referral can be made to a professional with the appropriate education and experience to help victims through the phases of healing.

Conclusion

Our society is one which downplays many risks including the risk of sexual assault. Publicity concerning sexual assault is often met with shock, horror and later, that familiar rationalization, "Well, it's not going to happen to me". Because of this, our society has been utterly paralyzed, until recently, with respect to providing facilities for the treatment and support of victims of sexual assault. Health services, including the establishment of sexual assault care centers, are now available in the larger cities of Ontario where physicians and other team staff can offer medical treatment and psychological support for victims of sexual assault. The present problem concerns expansion of

these facilities and increasing their availability in a climate of increasing financial restraints and cutbacks. In addition, greater initiative is needed to educate medical professionals and the general public about sexual assault and the Rape Trauma Syndrome to ensure that they are better informed about issues relevant to preventing and treating sexual assault. Physicians can significantly contribute to this objective with very little personal effort by having pamphlets and other literature on sexual assault available in their waiting rooms. These are readily available from the Ontario Women's Directorate. Until more information and training is available for physicians, however, they will be responsible to educate themselves about how to provide the best care to victims of sexual assault so that they may continue to fulfill their responsibility to cure sometimes, relieve often, and comfort always.

Acknowledgments

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Report from Israel: Impressions of a Children's Hospital

Sharon Sharir, B.Sc. (9T5)

Children's Medical Centre of Israel – Israel's newest hospital.

This past summer, I spent one month at the Children's Medical Center of Israel (CMCI) in the city of Petach-Tiqva, which is situated near Tel-Aviv. Being originally from Israel, I did not expect to find myself in a setting that was particularly unfamiliar. I presumed that apart from being conducted in Hebrew, hospital life would be much the same as it is in Canada. It was because of these expectations that the unique situations I did encounter were so striking.

CMCI is the newest hospital in Israel, having been completed about one year ago with money donated by an American businessperson. It was set up to serve as a modern children's medical centre for the entire Middle East. Given the political situation in the region, however, and the fact that all the countries in the region except Egypt are still officially at war with Israel, this was somewhat of an optimistic goal. Nonetheless, from time to time children do come from the surrounding Arab countries, though without the "official" knowledge of their governments.

Architecturally, CMCI is attractive and innovative in design, particularly in comparison with most Israeli hospitals, which were built purely with function in mind. It comprises a bright, spacious central atrium around which are situated the clinics and wards. Various elements have been incorporated to make it particularly suitable for children, such as a bright colour scheme, a play area on every floor, and open spaces, glass walls, and low dividers so that the children don't feel closed in. Furthermore, attempts are made to lessen children's anxiety about being in a hospital. Parents are accommodated in the rooms with armchairs that convert into beds, children scheduled for

surgery are given a tour of the area beforehand so that they know what to expect, and parents come into the operating room and remain until their child is asleep.

When I was first being shown around CMCI, I was proudly informed that the hospital was "American style" and was asked to confirm that it was indeed just like the ones we had back home in "America" (Canada exists as the 51st state in most Israelis' minds). I replied that while CMCI may resemble the hospitals in North America architecturally, the people in it identified it as clearly Israeli. The doctors were dressed in a typically informal style: short sleeved shirt; casual pants, skirt, or jeans; and casual shoes, runners, or - that most Israeli of footwear - sandals, often with socks. Some parents were sitting with their children and smoking a cigarette. Others were standing in front of the nursing station, arguing with the staff or making demands in very loud voices. They were in turn being ignored or argued with by the nurses, doctors, secretaries, and caretakers. While this sort of scene is commonplace everywhere in the country, having become accustomed to the relative calm and quiet of Canadian hospitals, I could not help but notice the difference.

Care at the bedside

I had the opportunity to experience how other hospitals differed from CMCI, though mercifully for only short periods of time, on those occasions when I went to the emergency department at Beilinson Hospital next door. Although the medical equipment there was relatively up-to-date, the paint on the walls was peeling and the air-conditioning was nonexistent. The room was noisy and crowded, with people lying on cots or sitting in what looked like makeshift wheelchairs composed of two wooden boards on wheels. On the wards things weren't much different. Rooms were crowded and contained four beds each, with no partitioning curtains between them.

Although in contrast CMCI was very modern, it still suffered from some of the problems that plagued other hospitals. One morning, while a visiting British surgeon changed into greens in an adjoining dressing room, we sat around the table in the OR lunchroom eating a typical "ten o'clock meal" (in Israel, one generally eats 4 to 5 times per day) of rye bread, cheese, olives, salad, hummus, and eggplant. Suddenly, the lights went out - a not infrequent phenomenon in any Israeli hospital. Although there is an emergency generator for essential areas such as the operating rooms, the lunchroom was not considered one of these. We continued to eat and talk in near-darkness until I suddenly remembered that the honoured guest was still in a pitch-black dressing room. He was too polite to make a fuss, as the rest of us would have done in his situation, and as a result was left to try and grope his way around in the darkness until someone went in and got him out.

The backgrounds of the children at CMCI reflected that of the population in Israel as a whole: Jews constitute approximately 85% of the population while Israeli Arabs, who are mostly Moslem but occasionally Christian, make up about 15%. Other groups such as Druze and Bedouin constitute even smaller minorities. In addition, there are a large number of Palestinians, who are Arabs that do not hold Israeli citizenship and who live in the West Bank and Gaza Strip. However, two groups of kids were overrepresented at CMCI - the religious Orthodox Jewish children and the Arab children. Both of these communities tend to have large families, so that proportionally more of their children end up at the hospital. These children also made up nearly all of the trauma cases on the floor, as older siblings who are often given charge of the younger ones are not always able to watch over them effectively. Most commonly, the children were involved in motor vehicle accidents, fell from balconies of apartment buildings or roofs, or were burned by hot soup or water. The latter was particularly prevalent on Fridays, occurring during preparations for the start of the Jewish Sabbath on Friday night.

As a result of the varied backgrounds of the kids, the staff had to learn to communicate with children and their parents in various languages. Although Hebrew was used most often, there were quite a number of Arab families who spoke little Hebrew, with their children generally speaking none at all. Many of the staff who were not fluent in Arabic had a rudimentary knowledge of the language, though this consisted mostly of slang expressions and commands such as "breathe". Thus, it was occasionally necessary to use translators such as an Israeli Arab staffperson, a Jewish nurse originally from Iraq, or another Arab child's parents. Sometimes it was even necessary for both parties to resort to speaking in a common foreign language - English - in order to communicate. On occasion, translators were also needed for members of the two most recent groups of Jewish immigrants, those from Ethiopia and those from the former Soviet Union.

Children's backgrounds represented a very important part of the medical history since different Jewish *edot* ("communities") have different diseases associated with them. Here in North America most Jews are Ashkenazi (i.e. of

Eastern European background), so it is well-known that Ashkenazi Jews have higher incidences of disorders such as inflammatory bowel disease, Tay-Sachs disease, and Gaucher's disease. In Israel, however, approximately half of the Jewish population is Sephardi (i.e. of Spanish-Portuguese, Middle Eastern, and North African background). In contrast to Ashkenazim, Sephardim have higher incidences of diseases such as familial Mediterranean fever and thalassemia, as do Arabs. On the other hand, Jews from Yemen are distinct in that they often have very low white blood cell counts. Thus, an apparently "normal" WBC in a Yemenite child may actually indicate a severe infection.

When in Israel, it is impossible to be unaware of the current political situation, since people are constantly discussing the latest developments. At the hospital it was no different, with the political realities of living in Israel being reflected in what went on there. The cafeteria in the basement had large steel and concrete doors and could function as a bomb shelter if necessary. During the recent Gulf War, however, it could not be used as it would not have offered protection against chemical weapons if they had been used. Instead, patients were discharged if at all possible and sealed rooms were set up on each floor for those children who remained. Medical emergencies heed no alarm sirens, however, and some of the doctors found themselves operating on children in the middle of SCUD missile attacks, hoping that the hospital would not be hit.

The ongoing Palestinian uprising *(intifadah)* also affected life at CMCI in various ways. Most tragically, this was reflected in the children who were injured as a result of the conflict. One of the children on the floor was a ten-year-old Palestinian boy from a village near Jerusalem. He had been a bystander during a clash between Israeli soldiers and protesting Palestinian youths, and was hit with a stray bullet which left him hemiplegic. Others were affected in different ways, such as the father who accompanied his comatose daughter after she fell from a balcony. He was a Palestinian from the Gaza Strip who came into Israel on a day permit for work, but was required to return to Gaza every evening because of general security measures. He was very concerned about his daughter, but was further worried because he did not have permission to remain with her overnight. Happily, the staff managed to arrange for an extension of his permit from the army, and he was able to stay and see his daughter make a remarkable recovery. This sort of bureaucracy also affected Jewish parents, such as the father of a boy who had recently undergone an appendectomy. He was supposed to start his one month army reserve duty the following day, something that all men do annually until age 50 (in addition to the two to four years served by both women and men after they graduate from high school). He spent the better part of a day trying to obtain a detailed letter from the hospital rather than just a form note, in the hope that he might be granted a deferral or exemption from army service. Ultimately, he was able to get an exemption from the first two weeks of duty.

Religious beliefs and practices were often evident at CMCI. Parents could be seen by their child's bed, praying quietly or wailing fervently in Hebrew or Arabic. Some children arrived in the OR with prayer books in their beds. Others came with a red string tied around their wrists, a traditional method of protection from the "evil eye". For the benefit of the Orthodox Jews, the kitchen which parents used to make meals for their children was a kosher kitchen - that is, it had separate sinks, counters, and dishes for meat and for dairy foods, in accordance with Jewish religious law. Of course, the fact that the Arab parents were unlikely to be aware of the Jewish dietary laws, coupled with the fact that the secular Jews there were aware but probably didn't care, made it unlikely that many Orthodox Jews used it after all.

With regard to the issue of consent, physicians were well aware of whose permission had to be obtained when dealing with an Orthodox Jewish child. This point was made clear to me on one occasion when an Orthodox boy was brought in by his mother with suspected appendicitis. As the necessary arrangements were being made, one of the doctors told the mother that if she needed to ask permission from someone to have the boy operated on, she should go and ask now. I was not impressed by what I perceived to be a need to ask permission from the father, rather than just consulting with him. Later on in the OR, one of the nurses asked the doctor if the go-ahead had been given to operate yet. The answer was that yes, the rabbi had agreed. I was stunned to learn that this was the person who had to be consulted before the appendectomy could be performed! As it turns out, Orthodox Jews always check with their

Triplet boys born at CMCI

rabbi before undergoing any major medical procedure. Surprisingly, even some secular Jews consult with them, as they are of the opinion that not only are the rabbis' judgements usually correct, but that they also have detailed knowledge of which physician is best for treating a given medical problem.

Near the end of my time at CMCI, an Orthodox woman who was pregnant with triplets was brought in for a Caesarean section so that the children could be taken directly to the neonatal ICU. She came into the OR clutching a prayer book and letters from her rabbi. She asked me to clip a picture to the sheet in front of her so that she could look at it during the operation. I obliged, and was surprised to see that the picture was not of her husband, as I had expected, but of her rabbi, the Lubavitcher rebbe from New York. She informed me that this was an entirely natural pregnancy; she was thirty years old and already had five children, all under seven years of age. The operation went well, with all three children in excellent health. My mind was still reeling from the implications of having eight children when she informed me that having a C-section was fine, but she wanted the next one delivered the "regular way"!

Spending a month in a hospital setting in Israel was both fun and fascinating. The staff at CMCI were very welcoming, and provided me with a tremendous opportunity to learn and participate in clinical medicine. At the same time, I was able to observe how Israel's many unique characteristics impact on the hospital experience and on the practice of medicine. Even for those who are well-acquainted with the country, a summer elective in Israel will undoubtedly prove to be an experience not quickly forgotten.

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Recent Advances in the Medical Treatment of Autism

Review of a Lecture by Dr. Luke Y. Tsai, at the 1993 International Conference on Autism

D'Arcy Little, Toronto, July 1993.

Jamie is a real handful for his parents . . . Just before he turned two, he started worrying them by banging his head repeatedly on the sofa. He shows extreme distress when things around him are changed even slightly: if the ashtray on the living room coffee table is moved from its usual central position, he launches into a fierce tantrum. Jamie also has a rather limited range of interests. He doesn't participate even in simple games with other children but instead spends countless hours lining up his collection of bottle caps in painstakingly straight lines. Another thing that concerns Jamie's parents is the fact that he doesn't come to them when he is sick or injured, and he resists their cuddling with a vengeance. They are at their wits' end and aren't sure where to turn . . .[1]

Jamie has many of the manifestations of Infantile Autism, a severe, lifelong, and pervasive developmental disorder which usually appears in the first 30 months of life. People with autism have serious problems with communication, social interaction and behaviour[2]. The confusion and lack of direction experienced by Jamie's parents are not uncommon. For many years, autism was mistaken for schizophrenia or mental retardation. Only now is this disorder becoming recognized by researchers and the public alike.

To shed further light on autism, the 1993 International Conference on Autism: A World of Options was held at the Regal Constellation Hotel in Toronto from July 13th to 17th. The conference attracted approximately 1500 participants from around the world. Among them was William Christopher, well known as Father Mulcahy of the hit TV series M*A*S*H, whose own son is autistic.

On July 15th, Dr. Luke Y. Tsai spoke to an overflow crowd about recent advances in the medical treatment of autism. Dr. Tsai was uniquely qualified for this. In addition to being a child psychiatrist and Director of the Developmental Disorders Clinic at the University of Michigan Medical Center who has worked and researched in the field of autism for over ten years, he is also the father of an 18 year-old son with autism. Dr. Tsai has also recently contributed two chapters on biomedical research in autism and medical treatment in autism to a book entitled "Autism: Identification, Education and Treatment"[3].

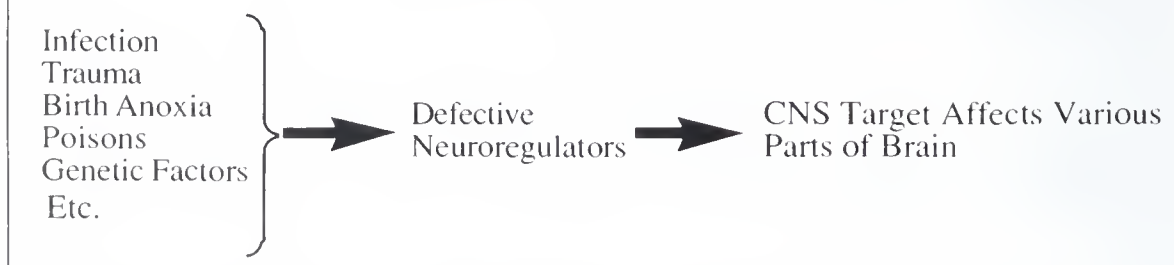
Dr. Tsai began his talk by reviewing some of the historical developments in the treatment of autism in order to be able to discuss the rationale for the therapies currently used. Since the early 1800's, the brain has been recognized as the important seat of behaviour. This knowledge was first exemplified in the study of phrenology which attempted to locate and measure areas on the skull and to interpret and predict normal and abnormal behavior in this way. Dr. Tsai drew a parallel to the present understanding of the brain. Neurotransmitters relay messages in neural pathways; if these pathways degenerate or are damaged, pathology results.

People with autism have serious problems with communication, social interaction and behaviour.

After carefully laying the framework for the biological basis of behaviour, Dr. Tsai emphasized that autism is not, as it was first described by Dr. Leo Kanner in 1943, a psychological problem caused by poor parenting , but is instead a neurological disorder. Although no single etiological agent has yet been discovered for autism, the medical model of the pathogenesis of autism considers several possible etiologies, such as infection, trauma, birth anoxia, poisons, and genetic factors. All are believed to lead to the common pathway of defective neuroregulators that have targets in the central nervous system (see Figure 1).

Since autism often affects three large, overlapping aspects of behaviour, it stands to reason that autism can often be localized to more than one region of the CNS (see Figure 2). Therefore, autism is best thought of and treated as a heterogeneous, behaviourally-defined syndrome[4].

Figure 1: Medical Model of the Pathogenesis of Autism



The syndromic nature of autism requires a comprehensive treatment program. The primary aim of this is to ensure physical and psychological health through such interventions as annual check-ups and immunizations, social and job skills training, speech therapy, auditory training, and

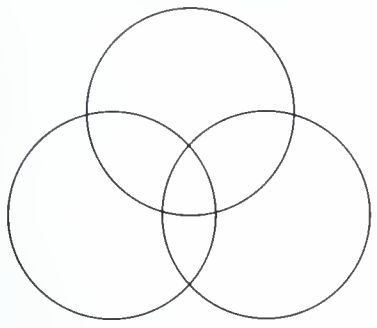

Restricted Interests and Activities,
Motor Disturbances (Stereotypy):
- basal ganglia pathology
Social Interaction Problems:
- frontal lobe pathology
Communication / Language Problems:
- left temporal / cortical pathology
- brainstem (hearing) problems.

Figure 2: Overlapping Aspects of Behaviour Affected by Autism and Their Possible CNS Localizations (adapted from an overhead of Dr. Tsai.)

educational assistance. The secondary aim of this program is to detect and treat maladaptive behaviours in order to increase the quality of life of the patient. Once the relationship between the behavioural abnormality and the underlying biochemical abnormality has been established, the goal of pharmacotherapy is to correct both with an effective chemical agent[5]. Dr. Tsai simplified this concept by stating,"If we think of the syndrome as autism plus 'collateral damage', where 'collateral damage' can be any one of attention deficit disorder, major depression, anxiety disorder, obsessive-compulsive disorder, tic/Tourette disorder, and schizophrenia etc., then the appropriate medication can be used to alleviate the 'collateral damage' (see Table 1)."

However, before drug treatment is initiated in children with autism, Dr. Tsai indicated that several basic principles of pharmacotherapy should be carefully observed. First, drug treatment should be based upon a sound diagnosis and should be reserved for children with severe impairments of emotional and social development. Second, medication should never be used as the sole intervention, and should always be part of a comprehensive treatment plan. Third, the child, the parents, and the school should be included in the treatment process to help gauge the response to the medication. Fourth, therapeutic gains need to be weighed carefully against side effects to minimize risk to the individual. Finally, drug administration should proceed at an optimal dosage for 2 to 6 months, at which time the drug should be discontinued to permit an evaluation of the need for continuation of the medication.

Dr. Luke Tsai's lecture provided a comprehensive account of the state of the art treatment of autism and was punctuated with anecdotes and humorous slides. Dr. Tsai commented that although he had worked in the field for over ten years and had an autistic son himself, each family he treated represented a new experience.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC, American Psychiatric Association, 1987: 38-9.
2. Autism Society of Ontario, What is Autism? Toronto, 1992.
3. Tsai, L.Y. in Berkell, D.E. (ed.): Autism: Identification, Education, and Treatment, Lawrence Erlbaum Associates, Publishers, New Jersey, 1992: 53-67, 151-182.
4. Ibid., 153.

Table 1: Medications for Treatment of Autism and Associated Disorders*:

"COLLATERAL DAMAGE:"	MEDICAL TREATMENT:
1. Hyperactivity/ Attention Deficit Disorder:	Ritalin: 0.3 - 1.0 mg/kg/day Dexedrine: 0.15 - 0.5 mg/kg/day Catapres: 0.15 - 0.6 mg/day
2. Stereotypies, Obsessions, Compulsions:	Haldol: 0.5 - 15 mg/day Prozac: <40 mg/day Anafranil 100 - 300 mg/day
3. Tic Disorders/Tourette Syndrome:	Haldol: 3 - 5 mg/day Catapres: 0.15 - 0.6 mg/day
4. Self- Injury:	Haldol: 0.5 - 15 mg/day Naltrexone: 1- 2.0 mg/kg/day
5. Aggressiveness:	Haldol: 0.5 - 15 mg/day ?Desyrel: <400mg/day
6. Withdrawal:	?Naltrexone: 0.5 - 2.0 mg/kg/day
7. Sleep Disturbances:	Catapres: 0.05 - 0.15 mg/night ?Desyrel: 50 - 150 mg/night ?Benadryl: 2.5 - 5.0 mg/kg/night
8. Depression, Irritability:	Prozac: <40 mg/day Tofranil: 1.0 - 5.0 mg/kg/day Norpramine: <5.0 mg/kg/day Desyrel: <400 mg/day
9. Phobic or Over-Anxious Reactions:	Buspar: <40 mg/day ?Tofranil: 1.0 - 5.0 mg/kg/day Librium: 45 - 90 mg/day
10. Delusions, Hallucinations:	Haldol: 0.5 - 15 mg/day
11. Enuresis:	Tofranil: 25 - 75 mg/night
12. Seizures:	Anticonvulsants: check blood levels regularly

*Table adapted from a handout given by Dr. Tsai, July 15, 1993.
?Uncertain effectiveness.

Annotated Bibliography of Women in Medicine.

Beverly C. Walters and Irene Y. McNeil.
211 pp. Ontario Medical Association, 1993.
Available from the Ontario Medical Association.

This annotated bibliography is an excellent resource for students, physicians and others interested in the area of women in medicine. It was compiled by Dr. Beverly Walters, a neurosurgeon at Sunnybrook Health Sciences Centre, and Irene McNeill, a research assistant in the Sunnybrook Research Design Office. The authors introduced the volume by explaining its roots, "our interest in the subject of women physicians came from the questions we heard young female medical students and residents asking about the difficulties of being female and being physicians." These questions generated discussion amongst women faculty and within this context came a request from colleagues to help with a survey of female surgeons in Canada. The purpose of the survey was to generate data that might encourage female medical students to consider a career in surgery.

The results of this survey were published in the Annals of Surgery and the authors were awarded the Royal College of Physicians and Surgeons Medal for Research in 1992, in recognition of the importance of the subject and the methodological strength of the research.

As the authors worked on the survey, they collected a wealth of references on the subject of women physicians. Walters and McNeill took the idea of formalizing and annotating the bibliography to the Ontario Medical Association's Women's Issues Committee. The OMA committee was receptive to the project and provided funding for the publication and distribution of the bibliography.

The result is an annotated bibliography which contains over 450 references spanning from 1938 to 1993. The references cover a substantial body of subjects, including the history of women in medicine, gender bias, undergraduate medical education, women in academic and organized medicine, lifestyles and stresses, role models, and many others. Each reference contains an abstract written either by the author of the paper or by Walters and McNeill in cases where the publication did not include one. The abstracts are very clear, concise and give the reader enough information to judge the usefulness of any particular article or book. The bibliography is very user friendly as each reference is listed in the bibliography twice: once in alphabetical order by first author, and again by main category.

The bibliography suffers only from its authors' failure to expand the annotations to research done outside of the medical establishment. While there was some attempt to include social science journals, most referenced publications were those of mainstream medical research. If the authors had broadened their comupterized literature search to include databases in women's studies, psychology and other disciplines, the bibliography could have been significantly expanded. There is a great deal of writing in feminist journals on women's health, some of which specifically addresses women as health care providers. I was disappointed to discover this research was overlooked in the bibliography. Researchers using this volume will unfortunately not benefit from insights gained in non-medical disciplines.

This criticism not-withstanding, the Annotated Bibliography of Women in Medicine is full of new and interesting articles. It is a valuable tool for researching a wide range of issues in the area of women and medicine.

Amy Freedman, B.Sc. (9T5)

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Reinders FX, Chalin C, and Meier HMR. Alzheimer's disease: Understanding the patient and caregiver. UTMJ 1993; 70(2): 16-20.

For further details, see CMAJ 1985;133:443-448.

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Illustrations - Each figure should be designed to fit into an area of either one or two columns of text. Photographs and illustrations must be in black and white and of good quality. Colour will only be considered if the author or an outside sponsor is willing to pay the cost. The figures, including halftones and photographs, are to be numbered consecutively in Arabic numerals, and each one must be referred to in the text. Captions should be succinct but with sufficient detail.

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Publication deadlines are September 15, November 15 and January 15. Papers which are submitted earlier will receive greater consideration.

Reprinted from UTMJ 1925; 2(7): 229-232, plus advertisements. The following is identical to the original publication and the facts and views expressed may not reflect current thoughts.

The University of Toronto Medical Journal

VOL. II MAY, 1925 NO. 7

EDITORIAL

CHARLATANISM

THE extraordinary prevalence in modern times of chiropractors, osteopaths, naturopaths, and others of like sort, has led to a search for suitable legislation for dealing with the situation. True, it has always been more or less so, and while we have not always had the "electro-therapeuths" and Christian Scientists with us, an older day has seen others just as bad. One doubts whether the time ever existed when a multiplicity of kidney pills and vegetable compounds was not offered to a long-suffering public. Nevertheless, the problem to-day is acute, and we are seeking a solution in legislation. Such legislation is eminently justified, for the state is as much obligated to protect its citizens from exploiters of health as from despoilers of wealth. Yet one sometimes wonders whether the situation can ever be met adequately until something more fundamental is done. To restrict the activities of the rogue is an evident duty, but to protect the public from a system, the dangers of which they do not appreciate, smacks too much of paternalism to thrive long in a democratic state.

The most remarkable aspect of the problem is not the prevalence of irregular healers, but the extraordinary gullibility of those to whom they appeal. Public information on many topics is good, but the most absurd propositions are propounded for the healing of mankind, and gain wide acceptance among intelligent and educated folk. It would seem that this guillibility in the matter of therapeusis is largely due to the monumental ignorance of the average person about his own body and about the methods of modern science. The average man is less informed about himself than about any other object in the universe, and very few, indeed, know that medical science is accumulated experience, and not multiplied theory. Hence, it appears that in education lies the best hope of saving a foolish people from their folly.

But the education must be specific. It must deal with physiology and general biology. Our generation is sorely in need of a modern Huxley to preach the value of biological science in education. It is certainly an unbalanced system which labels a man as "educated" who isn't sure whether or not he has a spleen, and who thinks his blood vessels are all veins. To teach a man the ancient lore of Greece is commendable; to instruct him in the languages of the earth is good; and to point out to

him the significance of the Renaissance is desirable, but he is never fully oriented in his environment until he knows something of himself. The children in our schools are practically never given any instruction in human physiology. They are never told, for instance, that nerves have definite known functions, and do not cause consumption and chilblains when pinched. Indeed, people frequently finish a college course and never seem to grasp the fundamental idea underlying scientific method. These deficiencies in public education explain why so many educated people fall victims to the charlatan's wiles.

Every school child should be taught something of physiology, something of biological science in general. He should be given at least a hint as to the scientific method of observation and experiment. Such instruction need not displace any other essential of education, and it need not be too extensive. Yet it should give the average person some little information about himself and his environment. Such instruction, insufficient in itself, would form a convenient foundation for the further education of the citizen by proper medical publicity, so that people might know at least as much about themselves as they know about locomotives. With a public thus intelligently informed, legislation against charlatanism would have the popular support it deserves, instead of having to be laboriously forced through parliamentary bodies. And what is even more important, the further progress of medical science would be assured of sympathetic support.

HOW TO PASS EXAMINATIONS

A SYSTEMATIC method of answering examination questions is an invaluable aid to the student in overcoming these annual obstacles to his progress. Indeed, a systematic approach to any question in medicine is an essential, whether one is writing, studying, practising, or teaching. Fortunately many medical problems lend themselves readily to such an appeal.

In treatment, for example, we have Dr. Rudolf's arrangement of (1) Diagnosis, (2) Environment, (3) Diet, (4) Symptomatic, and (5) Specific treatment.

Again, any question relating to the pathology or to disorders of an organ can always be most thoroughly answered by keeping in mind the causes of pathology, classified in some such way as (1) Congenital, (2) Traumatic, (3) Toxic, (4) Inflammatory, (5) New growths and cysts, (6) Vascular, (7) Parasitic, (8) Unknown, (9) Functional.

Symptoms may be classified as (1) related to the organ immediately involved, (2) related to neighbouring organs, (3) toxic, (4) reflex, and such an arrangement not only helps one to remember all the symptoms, but forces one to appreciate their true cause, and so indicates the proper symptomatic treatment.

Prognosis should be thought of in two parts, (1) immediate, (2) ultimate.

Diagnosis may be systematized by considering in order, (1) History, (2) Physical examination, (3) Special examinations, (4) Laboratory

Tests and X-ray, (5) Differential Diagnosis. Each one of these may also be systematically approached, especially the first two, whose routine is familiar to us all. With regard to special examinations, however, a routine is less usually practised, but is equally valuable. A suggested routine for the examination of a patient suspected of tuberculosis is outlined elsewhere in this issue. The routine of a thorough neurological, cardiological, genito-urinary and other examinations is equally important to know, and perhaps not sufficiently stressed in our teaching.

The same principles may be applied to all sorts of local examinations, as for example a recent fracture, or a breast suspected of cancer. In all cases the points to look for should be known and brought out in logical order by an established system of examination and questioning. The order in which the various points are considered may be important, but is not so important as that some systematic attack of the problem should be attempted, and that this attack should always be as much the same as possible. Herein lies the foundation of the habits of accuracy and thoroughness.

If lectures and clinics were always given from such a standpoint and with such method, the task of the student would be greatly lightened.

THE FUTURE OF THE JOURNAL

THE completion of the second year of life for THE UNIVERSITY OF TORONTO MEDICAL JOURNAL is a fit occasion for taking stock. At first distinctly an experiment, perhaps not exciting enthusiasm in every mind, THE JOURNAL has, we believe, made many new friends, and increased the confidence of many old ones during these two years. But the record of the past must stand alone, and no remarks which might be made here are capable of altering the verdict as to the merits and demerits of that record. To the future, however, it seems more profitable to turn our eyes, in the hope that a brief but rich experience may aid us in seeing what lies ahead.

We believe that THE JOURNAL will become more and more a medium for the publishing of student articles. In all probability, however, staff articles will continue to occupy an important place among its pages. From the very outset, certain friends advised that THE JOURNAL publish student articles exclusively. This seemed inadvisable, and undoubtedly the generous co-operation of numerous members of the staff has largely determined the success of THE JOURNAL. But this year 43% of the articles were by students, as compared to 20% last year. Thus it is established that a large proportion of the articles can be drawn, and drawn with profit, from students. And further, upon the contributions of undergraduates does the feasibility of the magazine depend.

THE JOURNAL will be a larger magazine in the future. Toward the end of the present academic year, the number of articles in each issue was materially increased, and, as a result, the sales were much better. To such an extent is this true, that within limits it is cheaper to publish a large Journal than a small one. And a more extensive table of contents will surely come nearer to satisfying every reader with something in which he is especially interested.

The circulation of THE JOURNAL will increase. Already many copies leave Toronto, and with a concerted effort to obtain a strong foothold in McGill, Queen's and Western, as well as among recent graduates and other practitioners, the number can be increased. The circulation among recent graduates is already considerable, since THE JOURNAL offers an excellent contact with the student's first source of medical information, no matter where he may live.

Besides these effects which the future will in all likelihood have upon THE JOURNAL, the publication will itself produce some definite results on medical student life at Varsity. The quality of student work will be raised by the encouragement offered to the production of papers on medical topics. The average student's knowledge of medical biography will be increased by a reasonable emphasis on that subject. The student, also, who begins by reading his undergraduate publication will be much more likely to continue reading periodicals after graduation. And finally, the experience gained by students in publishing the magazine can not but tend to make them in every way better educated men.

On the whole, one cannot but be hopeful. Certain difficulties will, of course, be encountered. The difficulty of appealing to the first two or three years is great, since a certain portion of THE JOURNAL is of necessity somewhat uninteresting to them. That problem must be solved by securing a large number of contributions from the men in these years. But THE JOURNAL, we dare to believe, is here to stay, and those of us who relinquish connection with her do so with profound regret, but also with supreme confidence in her future.

INTERNESHIPS FOR WOMEN

The changed attitude toward women in professions, and particularly the increasing willingness of the medical profession to admit women to its ranks, is reflected in the fact that 128 out of 524 hospitals on the approved list now state that they admit women internes. In 1923, 135 out of 510 hospitals on the approved list favoured the admission of women internes. The 128 hospitals now admitting women use a total of 1,385 internes, whereas only about 214 women graduate in medicine each year. Therefore, so far as the number of places open to women graduates is concerned, all should be able to find interneships, and a wide range of choice is provided for them.

—J.A.M.A. 84; 13, 966. (March 28, 1925).

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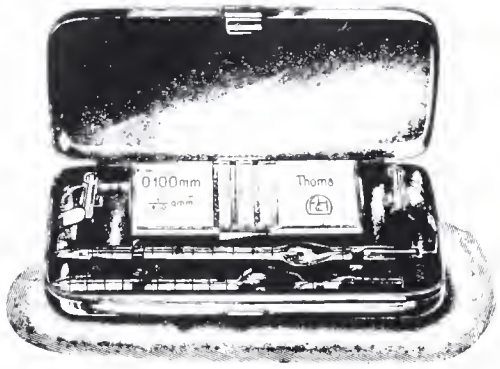

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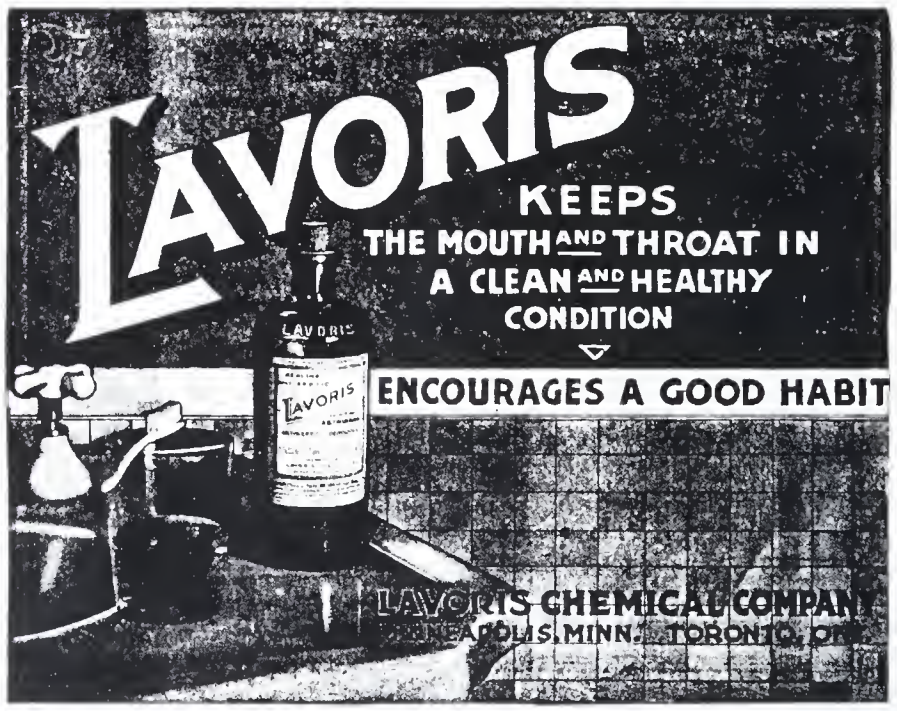

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